Lynn L. Bergeson
phone: 202.557.3801
lbergeson@lawbc.com

BERGESON & CAMPBELL PC

March 23, 2020

Via E-Mail

The Honorable Alexandra Dapolito Dunn
Assistant Administrator
Office of Chemical Safety and Pollution Prevention
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Dear Alex:

As legal counsel for the NMP Producers Group, Inc. (NMP Producers Group), I write for two reasons: First, to express again the NMP Producers Group's interest in finding a mutually satisfactory solution to the need to protect study reports submitted to the U.S. Environmental Protection Agency (EPA) for Toxic Substances Control Act (TSCA) Section 6(b) risk evaluation purposes from unnecessary disclosure, and second, to respond to certain statements included in the appended March 9, 2020, letter from Mr. Mark A. Hartman to Kathleen M. Roberts, NMP Producers Group manager. For the reasons noted below, the NMP Producers Group is most anxious to find a mutually acceptable solution to the concerns the Group has expressed in multiple communications with EPA staff in the Office of Chemical Safety and Pollution Prevention regarding the issue of study report protection and expresses its hope that you will engage directly to help find a mutually satisfactory solution to this issue. Because it is helpful to address the statements in Mr. Hartman's letter to contextualize the Group's repeated efforts to find a solution to this problem, we first address the statements in Mr. Hartman's letter that require clarification.

Statements in the March 9, 2020, Letter That Require Clarification

As a preliminary matter, we appreciate that you and your staff are extraordinarily busy, and we as a regulated community are grateful for all that you and your staff have done to implement TSCA. The current challenges we all face due to the COVID-19 pandemic add a layer of stress and uncertainty that none of us welcomes, but we all must address, as TSCA deadlines loom large.

Several points in Mr. Hartman's letter require clarification. They are presented in the order they appear in the response.

2200 Pennsylvania Avenue, NW, Suite 100W
Washington, DC 20037-1701
phone: 202.557.3800
fax: 202.557.3836
www.lawbc.com

ED_006308_00000213-00001

1. Verification of Methodological Details

Mr. Hartman's letter expressed EPA's view that a full study report provides EPA an opportunity independently to verify the accuracy of methodological details, verification that, in Mr. Hartman's view, the robust study summary cannot provide. While we would agree that a full study report would provide the best opportunity for verification, we do not agree that it is the only opportunity, and the letter offers no basis for this conclusion. The methodological details reported in the robust study summary are extracted directly from the study report. Having considered the matter extensively, we cannot identify a single component in a study report that would not otherwise be included in a robust study summary that allows for independent verification of the information listed.

2. Fertility and Fecundity Indices Cannot Be Calculated Using Individual Animal Data

The NMP Producers Group conferred with Dr. Willem Faber, a well-known and internationally respected reproductive toxicologist, regarding EPA's claim that the individual animal data do not provide the information needed to calculate fertility and fecundity indices for the parental generation. Dr. Faber confirmed that he had no problem locating the relevant individual mating assignments for the F1B, F2A, and F2B generations in the raw data provided to EPA. He was able to make the fertility and fecundity calculations based on the information provided in the NMP Producers Group submission. We would be pleased to assist EPA further in this regard, but we do not agree that fertility and fecundity indices cannot be calculated using individual animal data and, more to the point, neither does Dr. Faber.

3. EPA's Characterization of the 1991 Exxon Study as "High Quality" Is Demonstrably False

Mr. Hartman's letter states that EPA is in possession of an unnamed high-quality study on reproductive toxicity associated with N-methyl-2-pyrrolidone (NMP). The NMP Producers Group assumes that this unnamed study is the 1991 Exxon study, a study that we know EPA is using as a basis for the ongoing risk evaluation. The NMP Producers Group has previously provided detailed information that explains why this study, by any objective standard, cannot reasonably be considered "high quality" by EPA or by any other entity. For reasons we do not understand, however, EPA has declined to respond to any of the data quality concerns the NMP Producers Group has expressed to EPA on multiple occasions.

For your convenience, we attach the December 2019 and January 2020 NMP Producers Group submissions to EPA, both of which carefully explain the reasons why we object to the characterization that the Exxon study is "high quality" and why any reasonable person would similarly object to this characterization. As the sponsoring authority for NMP at the Organization

for Economic Cooperation and Development (OECD) Screening Information Dataset (SIDS) Initial Assessment Meeting (SIAM) in 2007, EPA was well aware that the international regulatory authorities rated the Exxon study (reliability score of 2) "inferior" in quality to those conducted by the NMP Producers Group (reliability scores of 1) (OECD 2007). EPA was also aware that the higher quality NMP Producers Group studies refuted the EPA contention that NMP produced biologically (not statistically) significant effects on fertility in the second generation of the Exxon study, which is now the key chronic toxicity end point selected by EPA in its revised NMP risk assessment. Given this indisputable international consensus on study quality and results, we are unable to reconcile EPA's reversal of its "inferior-quality" rating for the Exxon study at SIAM in 2007 to its more recent "high-quality" rating and the change this reversal had on the selection of the key chronic toxicity end point for NMP. The data did not change, only EPA's view of them did, for no explicable reason.

EPA's Meaningful Engagement in Dialogue on Study Report Protection Is Needed

Since it received the study report request from EPA in July 2019, the NMP Producers Group has offered, in good faith and on multiple occasions, creative, and in our view, thoughtful approaches to address EPA's request for the data while maintaining protection of the NMP Producers Group members' intellectual property rights. Unfortunately, each such approach has been rejected outright, without comment or explanation. It is even more disappointing that EPA's summary rejection has taken weeks, if not months, to be shared with the NMP Producers Group, greatly delaying the ultimate resolution of this important issue. Regrettably, since July 2019, EPA has offered not a single alternative proposal, nor has it engaged in any meaningful dialogue intended to find a mutually satisfactory solution to this issue.[1] The single, and unhelpful, option that EPA has offered over the past nine months is for the NMP Producers Group to submit "complete, unredacted versions" of the study reports, the very act the Group is trying desperately to avoid.

You and others at EPA have rightly and publicly recognized the property rights issues at stake, and we appreciate that acknowledgement and support. Curiously, however, EPA's

---

[1] The one modest exception to this blanket rejection was EPA's suggestion that the NMP Producers Group express its study ownership rights regarding reports submitted to EPA to avoid further use by third parties without authorization. We have noted, however, that EPA's claims that others have used this approach with success has not been validated. We are unaware that EPA conducted a comprehensive analysis of whether these reports have been submitted to other regulatory jurisdictions, and, if so, how those government agencies have responded to the submissions. Similarly, we are unaware that EPA has determined what parties have downloaded the reports in question, or whether EPA has followed up with those parties to determine how the reports will be used.

actions have fallen far short of what we regard as engagement in a constructive dialogue focused on finding a solution.

EPA's Request for "Unredacted" Reports Does Not Align with Other Guidance

EPA's March 9, 2020, letter states that EPA must have complete, unredacted study reports to consider them in EPA risk evaluations under TSCA Section 6(b). We are perplexed by this demand, as it does not align with what we know EPA staff has advised other industry groups in similar circumstances. We are aware, for example, that EPA staff has informed industry representatives that EPA has accepted sanitized health and safety reports that redact certain information on testing facility (name, address, and study identification number), study staff, and dates. If this approach is acceptable, we question why EPA neglected to mention this to us as a viable approach months ago. If this approach is not suitable for the NMP Producers Group, EPA needs to explain why.

We also note that this approach does not align with EPA's supplemental notice of proposed rulemaking, "Strengthening Transparency in Regulatory Science." There, EPA states that there will be situations in which EPA will rely on data in its evaluations even though there is no public access to the data (*see* 85 Fed. Reg. 15405). The supplemental proposed rule also allows entities to provide redacted documents to keep confidential certain identifiable information.

We Renew Our Desire to Find a Workable Solution

As we have repeatedly stated in our many communications with EPA over the past nine months, the NMP Producers Group wishes to be responsive to EPA's request while protecting its legitimate interest in its intellectual property rights. We seek EPA's meaningful comments on the options we have offered to EPA. The NMP Producers Group wishes to share the study reports with EPA, but as responsible product stewards, we seek assurance that EPA will accept the reports even though they are not entirely "unredacted." If EPA nonetheless cannot provide that assurance, we seek a coherent explanation why it cannot.

As we have always believed this challenge is amenable to resolution, we offer one additional proposal, one that has been raised previously with EPA staff but to which EPA has yet to respond. Under this proposal, the study report would be provided to EPA as requested and without redaction, but would not be posted in the public docket. Instead, the robust study summary would be posted and made publicly available. If an outside stakeholder requested access to the study report, it would be provided to the requestor upon their execution of a non-disclosure agreement with the report submitter, stating that the report would not be used for commercial purposes. This approach provides EPA with the information it needs, allows access to those wishing to evaluate the veracity of the posted robust study summary, and protects the rights of the study report owner.

We are keenly aware that there is a time frame in which an agreement must be met under which EPA can consider the data from the NMP Producers Group's study reports, although EPA has not defined what that is. We respectfully request that EPA not defer a response to this letter for weeks and instead respond in a time frame that allows for follow-up action before this undefined deadline passes.

Thank you for your consideration. We are available to speak with you to discuss this issue further if you would find additional discussion helpful.

Sincerely,

Lynn L. Bergeson

cc: Tom Tyler, Esquire, EPA
Tala Henry, Ph.D., EPA

Attachments

NMP

N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

2200 PENNSYLVANIA AVENUE, N.W., SUITE 100W, WASHINGTON, D.C. 20037 • (202) 557-3800 • FAX (202) 557-3836

MANAGED BY B&C® CONSORTIA MANAGEMENT, L.L.C.

December 20, 2019

Via E-Mail

Mr. Mark A. Hartman
Deputy Director for Management
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1200 Pennsylvania Ave, NW (MC 7403M)
Washington, DC 20460

Re: EPA Request for Submission of NMP Study Reports -- Following Up on December 11, 2019, EPA Response to NMP Producers Group

Dear Mr. Hartman:

The N-Methylpyrrolidone (NMP) Producers Group submits this letter and the appended documents in response to your December 11, 2019, letter. The NMP Producers Group appreciates your and other U.S. Environmental Protection Agency (EPA) staff's efforts in addressing our concerns related to members' desire to protect their proprietary interests in the studies being requested by EPA. Unfortunately, your letter offered no workable solutions to the NMP Producers Group situation. We note again that the NMP Producers Group situation is not unique and that many other industry groups engaged in Toxic Substances Control Act (TSCA) actions have similar concerns on study report protection. We urge EPA to work with us and others to find a viable solution that will reasonably meet stakeholders' needs.

According to your letter, if the NMP Producers Group provides the full reports for the studies in question, EPA is unable to ensure that the reports will not be publicly disclosed. You state that this inability to protect the reports is due to EPA's interpretation of TSCA Section 14 and requirements under the Freedom of Information Act (FOIA). The NMP Producers Group has not conducted a legal analysis of EPA's positions and will not be commenting on them in this letter. We may, however, choose to challenge these positions in the future.

Your letter also invited NMP Producers Group members to consider including an assertion of ownership rights with any report submitted to EPA to avoid further use by third parties without authorization. You further state that "(o)ther study owners have taken such an approach and found success in similar circumstances…." While we appreciate EPA's suggestion, we question on what exactly EPA bases its claim of "success" by other study owners. Has EPA conducted a comprehensive analysis of whether these reports were submitted to other regulatory jurisdictions, and if so, what those government agencies' responses were? Does EPA

ED_006308_00000213-00006

know what parties have downloaded the reports in question, and has EPA followed up with those parties on how the reports will be used? We anticipate the answers to these questions is "no," and we are aware of no independent, empirical evidence to support EPA's optimism.

EPA must under TSCA use the *best available science* in its NMP risk evaluation. To comply, EPA must consider the data generated in the two reproductive toxicity studies sponsored by the NMP Producers Group (NMP Producers Group, 1999a and 1999b). This point was reinforced by members of the Science Advisory Committee on Chemicals (SACC) during its review meeting on December 5 and 6, 2019. Your December 11, 2019, letter states that EPA is already in possession of a "high-quality" study on reproductive toxicity and implies that the NMP Producers Group data are not necessary. Although not specifically stated in your letter, we assume the "high-quality study" that you are referring to is the Exxon 1991 study on which EPA has proposed relying for identifying the critical end point in the draft NMP risk evaluation. We note that the Exxon study cannot be considered a "high-quality" study for the following reasons:

- The mating schedule in the Exxon 1991 study was problematic because the animals had differing numbers of opportunities to mate. This method of breeding does not encounter problems as long as there is not a higher than normal incidence of infertile male or female rats within the test population. This was not the case with the Exxon 1991 study. The revised EPA Test Guidelines recognize that fertility is a "couples-specific" phenomenon and can only be evaluated based on single mating pairs, rather than multiple opportunities to mate with several partners.

- Complicating the mating schematic used in the Exxon study was the increased probability of brother:sister matings, given that both the male and female rats used in this study came from the same room within the same breeding facility.

- Additionally, the specific Charles River site where the rats from the Exxon study originated had fertility problems at the same time (fall of 1989) that the study was ongoing.

- By the end of the first (P1) generation, the number of females available for mating at each dose level group had dropped from 30 at the start of the study to between 13 and 16 at the start of the P2 generation. Even in the control group, there was a 47% reduction in females available for mating over the course of one generation. This suggests that there was something seriously wrong with this population of test animals.

- To generate the protocol-required group size of 30 males and 30 females, the study director needed to select more than 2 males and 2 females from certain litters from the 500 mg/kg/day group.[1] While this is a relatively minor point, it illustrates several points of concern. First, it becomes much more difficult to avoid brother:sister matings in the P2 generation within the 500 mg/kg/day group. Second, due to the smaller number of animals available for breeding, the overall population of animals in the P2 generation is becoming more inbred and therefore more likely to experience reproductive failure.

- In addition, during the course of the study, laboratory personnel did not detect the mating of some animals. The authors of the Exxon study did not include pregnant females for which mating confirmation had been missed by personnel within the fertility and fecundity indices. This indicates that some animals were fertile (as they were pregnant or the females they were paired with were pregnant) but were not included within the calculations simply due to the fact that the laboratory personnel did not detect the mating of the animals. The lack of inclusion of non-confirmed mated females who were pregnant and the use of multiple matings to different animals suggests that the calculations used to prepare the mating and fertility indices for this study are questionable.

- EPA, as the sponsoring authority for NMP at the Organization of Economic Development and Cooperation (OECD) SIDS Initial Assessment Meeting knows that the international regulatory authorities rated the Exxon study (reliability score of 2) inferior in quality to those conducted by the NMP Producers Group (reliability scores of 1).

- Most importantly, EPA's position that the fertility/fecundity effects in the Exxon study are "biologically significant" is not supported by the two additional two-generation reproductive toxicity studies sponsored by the NMP Producers Group, which had the higher quality ranking score, nor is it supported by the other studies cited by EPA as providing such support (Sitarek *et al.* 2012 and Sitarek and Stetkiewicz 2008).

---

[1] In the 500 mg/kg/day group, there were only 13 litters, and therefore only 26 male and 26 female rats in this group were available for selection to populate the P2 (F1b) parents, even though the protocol called for 30 each.

The NMP Producers Group voluntarily conducted the two additional reproductive toxicity studies to improve the available information on NMP, and we want EPA to use the information generated in its risk evaluation. It was always the Group's intent that the data would be considered for applicable regulatory purposes. We continue, however, to request that the study reports be protected. Members should not be forced to choose between the consequences of EPA's failure to comply with the law and sacrificing the Group's legitimate rights to confidentiality.

As we have noted in prior communications with EPA, the findings of these study reports are not claimed as confidential. Indeed, the reports in question have robust summaries of the testing program, and the key data points and scientific conclusions are prepared and publicly posted. It is not the information in the study report that needs to be protected from public dissemination. It is the study report itself that has the monetary value, as it is required for registration purposes in other government jurisdictions but is not publicly posted.

While we do not agree with EPA's position on public sharing of the study report, we do believe that there is another option. The NMP Producers Group is willing to share the relevant raw data from the study for EPA assessment purposes. These data, coupled with the robust study summary, should be sufficient for EPA and other knowledgeable stakeholders to judge the quality of the studies and the conclusions reached. The relevant information will be available to those with expertise to make meaningful and informed judgments on the study results.

To progress this important dialogue, the NMP Producers Group is proactively providing you with the robust study summary and raw data for the following study of interest to EPA:

- NMP Producers Group (1999a). Two-generation reproduction toxicity study with N-Methylpyrrolidone (NMP) in Sprague-Dawley rats -- Administration in the diet. Huntingdon Life Sciences, East Millstone, NJ, Project No.: 97-4106, unpublished report.

  The raw data pulled from the report in question includes

  - Individual male and female findings,
  - Organ weights,
  - Corpora lutea and ovarian follicular counts,
  - Pup observations, and

ED_006308_00000213-00009

- Tables for
  - Mating indices, pregnancy rates, and male fertility indices;
  - Gestation length, parturition data, and litter data;
  - Pup body weight -- data during lactation;
  - Pup and litter survival indices; and
  - Pup sex distribution data.

If EPA finds this submission acceptable for TSCA purposes, the NMP Producers Group would be pleased to provide the summary and data from the other study in question.

The NMP Producers Group would appreciate EPA's prompt consideration of this approach as it has implications on how the Group will proceed related to its comments on the draft risk evaluation. If needed, we would be pleased to meet with you to discuss this approach further.

Respectfully submitted,

Kathleen M. Roberts
NMP Producers Group Manager

cc: David B. Fischer, Esquire (EPA)
Stanley Barone, Jr., Ph.D. (EPA)
Ana Corado (EPA)

Attachments

Reference List

Exxon Biomedical Sciences. 1991. Multigeneration rat reproduction study with N-methylpyrrolidone. Project No. 236535, Nov. 26. Wayne, NJ: GAF Corp.

NMP Producers Group. 1999a. Two generation reproduction toxicity study with N-methylpyrrolidone (NMP) in Sprague Dawley rats: Administration in the diet. (Project No. 97-4106). Millstone, NJ: Huntingdon Life Sciences.

NMP Producers Group. 1999b. Two Generation Reproduction Toxicity Study with N-Methylpyrrolidone (NMP) in Wistar Rats - Administration in the Diet. (Project No. 70R0056/97008). Ludwigshafen, Germany: Department of Toxicology of BASF Aktiengesellschaft.

OECD. 2007. SIDS initial assessment report on 1-methyl-2-pyrrolidone. Washington, DC: Organization for Economic Cooperation and Development.

Sitarek, K., Stetkiewicz, J. 2008. Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats. Int. J. Occup. Med. Environ. Health 21(1): 73-80. doi: 10.2478/v10001-008-0006-z.

Sitarek, K., Stetkiewicz, J., Wąsowicz, W. 2012. Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. Birth Defects Res. B Dev. Reprod. Toxicol. 95(3): 195-201. doi: 10.1002/bdrb.21001.

NMP

N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

2200 PENNSYLVANIA AVENUE, N.W., SUITE 100W, WASHINGTON, D.C. 20037 • (202) 557-3800 • FAX (202) 557-3836

MANAGED BY B&C® CONSORTIA MANAGEMENT, L.L.C.

January 21, 2020

Via Docket Submission

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPT)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Comments on Draft Risk Evaluation for N-Methylpyrrolidone (EPA-HQ-OPPT-2019-0236)

Dear Sir or Madam:

The N-Methylpyrrolidone (NMP) Producers Group[1] is submitting these comments in response to the draft 2019 U.S. Environmental Protection Agency (EPA) risk evaluation on NMP (EPA 2019a) under Section 6 of the Toxic Substances Control Act (TSCA) ((84 Fed. Reg. 60087 (Nov. 7, 2019)). Our comments are organized in the same general order and format as the EPA charge questions presented to the Science Advisory Committee on Chemicals (SACC) for its review on December 5 and 6, 2019.

Environmental Fate and Exposure (Sections 2.1 and 2.2 of the Draft Risk Evaluation)

The NMP Producers Group has no specific comments or concerns on these sections. We agree with EPA's conclusions that NMP is not expected to persist in the environment and has a low bioaccumulation potential.

Environmental Hazard and Risk Characterization (Sections 3.1 and 4.1 of the Draft Risk Evaluation)

The NMP Producers Group has no specific comments or concerns on these sections. We agree with EPA's conclusions that NMP does not present environmental risks.

[1] The NMP Producers Group includes domestic manufacturers of NMP and was formed to address efficiently and comprehensively regulatory and stewardship issues pertinent to NMP.

ED_006308_00000213-00012

Occupational Exposure (Section 2.4 of the Draft Risk Evaluation) -- EPA Must Use NMP-Specific Protection Factor Values for Gloves

As further detailed in the appended Summit Toxicology report, "Critical Review of USEPA's Draft Risk Evaluation for N-Methylpyrrolidone" (Summit report, Appendix 1), EPA should not rely on default glove protection factors (PF) in the draft 2019 risk evaluation, as this assumption ignores available NMP-specific data that show the permeation rate of NMP can vary by more than three orders of magnitude, depending upon the material used in the gloves (nitrile ~ latex > polyethylene > butyl ~ laminate) (Zellers and Sulewski 1993; Stull *et al.* 2002; Crook and Simpson 2007). The default PF approach used by EPA significantly underestimates the degree of protection afforded by polyethylene, butyl, and laminate gloves.

The NMP Producers Group remains concerned that while this glove information was shared with EPA in July 2015 in a report, "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP Containing Paint Strippers," it was not apparently considered for the draft risk evaluation, nor was it put into the public docket as the Group requested.[2] To ensure that this important information is available and included in the final risk evaluation, the report will soon be published as open access in the *Journal of Exposure Science and Environmental Epidemiology* (JESEE). We will inform EPA as soon as the publication is available.

The proposed margin of exposure (MOE) value for chronic non-cancer paint remover applications using gloves in the EPA 2019 assessment is 6, which is the lowest risk value for the use categories reviewed (Table 4-50).[3] This scenario utilized a glove PF of 10 for exposures to liquid, neat NMP. Based on an analysis of chemical-specific data for NMP permeation through glove materials, the PF for highly protective glove materials is expected to be much higher than 10 (approximately 720 for liquid, neat NMP considering the impact on internal area under the curve (AUC) (Kirman 2020). Because the MOE for the high-end paint removal scenario is driven by the dermal absorption pathway for liquid NMP, the use of NMP-specific values for glove PFs is expected to result in an MOE of 30 and therefore would not present unreasonable risk. We should expect that the other use applications in the draft 2019

---

2 July 17, 2015, e-mail from Kathleen Roberts to Doug Parsons.

3 The NMP Producers Group notes that the draft 2019 assessment includes one risk estimate lower than 6. That risk estimate value of 4 is for "Use in Electrical Equipment, Appliance and Component Manufacturing." As further articulated in comments from the Semiconductor Industry Association (SIA) and others, EPA's assumptions on worker exposure controls for this industry sector are not aligned with ongoing workplace practices and need to be re-evaluated.

evaluation, with proposed risk estimate values greater than 6, would also be above the MOE of 30 after incorporating the NMP-specific glove PFs and therefore would also be considered as not presenting unreasonable risk.

EPA Provides No Evidence to Assume That OSHA Regulations Will Be Ignored

It is inappropriate, and EPA has provided no evidence, to assume that industrial and commercial NMP users will ignore their enforceable legal obligation under the Occupational Safety and Health Act (OSH Act). Yet EPA bases its risk evaluation precisely on this unsupported assumption.

In the various occupational scenarios, EPA estimates exposure levels associated with different levels of glove protection, varying from no gloves, to gloves not specific to NMP, to gloves that are protective for NMP. The General Duty clause of the OSH Act, among other provisions, requires every employer to furnish to each of its employees a workplace free from recognized hazards that cause, or are likely to cause, death or serious physical harm. This requirement includes a determination by the employer on appropriate glove types that are impervious to the substance used under the conditions of use, eye protection, and respiratory protection for employees where such protection is otherwise necessary to protect employee health. As such, facilities using NMP are required to conduct an evaluation as to which gloves provide the appropriate protection for NMP. It is therefore inappropriate for EPA to assess scenarios in which no gloves or the wrong glove types are used.

Occupational Safety and Health Administration (OSHA) data support the position that workers use appropriate gloves and other personal protective equipment. In an assessment of the 12 million record database of violations issued by OSHA dating back to the 1970s, the TSCA New Chemicals Coalition (NCC) determined that less than one percent of violations related to lack of eye protection, lack of general dermal protection, and lack of glove use (or inappropriate glove use), despite the fact that these violations are relatively easy to observe. Thus, while there may be some entities that are in violation of OSHA rules, those are a very small minority and should not be the driving force in determining whether unreasonable risk exists.

Exposure and Releases (Section 2.4 of the Draft Risk Evaluation)

Csat/Air Concentration Values Are Inconsistent, Do Not Reflect Real-World Scenarios

As detailed in the appended Summit report, the values cited and used by EPA in its assessment are very conservative, inconsistent, and unrealistic.

ED_006308_00000213-00014

- In its application of the Consumer Exposure Model (CEM), EPA relied on the value of 1,013 mg/m^3 for the saturation of air by NMP (saturation concentration (Csat)) to predict air concentrations of NMP for consumer exposure scenarios. This value reflects a theoretical worst-case assumption of very low humidity that is inconsistent with the use of NMP in aqueous products with limited ventilation (*i.e.*, water in the NMP products is expected to increase room air humidity as both water and air volatilize from applied surfaces).

- EPA's assessment does not consider condensation and aerosol droplet formation for concentrations of NMP vapor exceeding 470 mg/m^3 (or 116 ppm) (Solomon *et al.* 1995, Saillenfait *et al.* 2003).

- We note that EPA used a Csat value of 640 mg/m^3 in its 2015 risk assessment but provides no explanation as to why that value is not used in the 2019 draft assessment.

- EPA needs to correct the Csat value for high-end engine degreaser and general degreaser scenarios, which was listed as 1,840 mg/m^3 in the EPA supporting spreadsheets.

- The relative magnitude of the air concentrations modeled for consumer exposures (*e.g.*, peak concentrations up to 1,300 mg/m^3; 24-h time-weighted average (TWA) up to 103 mg/m^3) compared to worker exposures (e.g., 8-h TWA up to 64 mg/m^3) is counterintuitive. Consumers would not be using NMP products over a 24-hour period. In fact, EPA used 810 minutes (or 13.5 hours) as the highest use duration in consumer conditions of use. The fact that the modeling shows consumers to have a higher air concentration over a 24-hour period than a worker over 8 hours indicates a problem.

In addition to the Summit report recommendations that EPA incorporate data on relative humidity distributions in the United States and evaluate aqueous versus non-aqueous NMP products separately, the NMP Producers Group asks EPA to carefully review the inconsistency of the values from the exposure models used for CEMs versus those used for worker exposures (Chemical Screening Tool for Exposures and Environmental Releases (ChemSTEER)) as there seem to be fundamental differences in the underlying assumptions.

ED_006308_00000213-00015

Many Exposure Assumptions Overestimate Actual Exposures

To ensure that the range of expected exposures to NMP by consumers is accurately characterized, EPA should modify its assessment as follows:

(1) For all consumer exposure scenarios, exposure scenarios should account for the most likely exposure scenarios, which involve product use in outdoor and/or garage settings (Abt 1992);

(2) For the small, unventilated room scenarios, two additional options should be included to account for higher air change rates associated with "Window Open" and "Exhaust Fan On"; and

(3) For consumer and worker exposure scenarios that are inconsistent with product labeling instructions, these should be labeled and presented separately as "Product Misuse Scenarios" so that risk management options for these scenarios can be addressed independently from "Product Use Scenarios."

Human Health Effects (Section 3.2 of the Draft Risk Evaluation)

EPA Must Consider Reproductive Toxicity Data from the NMP Producers Group for the Chronic Toxicity End Point

TSCA mandates that EPA must under TSCA use the *best available science* in its NMP risk evaluation. To comply, EPA must consider the data generated in the two NMP Producers Group reproductive toxicity studies (NMP Producers Group 1999a, 1999b). This point was reinforced by members of SACC during its review meeting on December 5 and 6, 2019.

The report, "Comparison of Fertility and Fecundity Results from Three Two-Generation Reproductive Toxicity Studies Evaluating N-Methyl 2-Pyrrolidone," which was prepared by Dr. William Faber and submitted to EPA by the Lyondell Chemical Company (Faber report), concluded that the animals tested under the NMP Producers Group studies (NMP Producers Group 1999a, 1999b) more accurately represent the true sensitivity to NMP-related effects of fertility/fecundity in rats than the Exxon 1991 study. Those studies, as noted, did not show the effects seen in the Exxon 1991 study. The NMP Producers Group notes that Dr. Faber is a well-known, respected toxicologist with decades of experience and fully supports his report.

The NMP Producers Group voluntarily conducted the two additional reproductive toxicity studies to improve the available information on NMP, and we want EPA to use the information generated in its risk evaluation. It was always the Group's intent that the data would be considered for applicable regulatory purposes. We continue, however, to request that the study reports be protected. Members should not be forced to choose between the consequences of EPA's failure to comply with the law and sacrificing the Group's legitimate rights to confidentiality.

On December 20, 2019, the NMP Producers Group engaged in additional communications with EPA leadership on other approaches that could be used to provide EPA and other knowledgeable stakeholders with sufficient information to judge the quality of the studies and conclusions to ensure that meaningful and informed judgments can be achieved, while protecting the Group's property rights. In that communication, we indicated the need for prompt consideration of the alternative approach, given the comment deadline for the EPA risk evaluation. While we remain hopeful for a positive outcome, we are disappointed that EPA has not provided any feedback to date. The NMP Producers Group is following up on its December 20, 2019, communication to EPA in a separate submission, which will also be posted to the docket.

EPA Cannot Lawfully Rely on the Exxon 1991 Study as the Basis for the Chronic Toxicity End Point

In the draft 2019 risk assessment, EPA proposes that the reproductive toxicity end point of decreased male and female fertility be the basis for human health risks associated with chronic exposure and relies on effects in the Exxon 1991 study. This approach is different than the one taken by EPA in its 2015 risk assessment on paint removers containing NMP, in which EPA relied on the NMP Producers Group studies and used fetal body weights (bw) as the end point.

The 1991 Exxon study cannot be considered a high-quality study and should not be the basis for EPA's human health risk assessment. The NMP Producers Group directs EPA to "Appendix A -- An Explanation of the Breeding Problems in the Exxon 1991 Two-Generation Study Evaluating NMP" in the Faber report for details on the points noted below:

- The Exxon study had increased probability of brother:sister matings, given that both the male and female rats used in this study came from the same room within the same breeding facility.

- The specific Charles River site where the rats from the Exxon study originated had fertility problems at the same time (fall of 1989) that the study was ongoing.

- The reduction of females available for mating at the start of the P2 generation, including those in the control group, suggests that there were reproductive problems with this population of test animals.

- As a result of the study director selecting more than two males and two females from the 500 mg/kg/day group to generate the protocol-required group size of 30 males and 30 females[4], it became more difficult to avoid brother:sister matings in the P2 generation within the 500 mg/kg/day group, and the overall population of animals in the P2 generation became more inbred and therefore more likely to experience reproductive failure.

- During the course of the study, laboratory personnel did not detect the mating of some animals, and the authors of the Exxon study did not include pregnant females for which mating confirmation had been missed by personnel within the fertility and fecundity indices. This fact indicates that some animals were fertile (as they were pregnant or the females they were paired with were pregnant) but were not included within the calculations simply due to the fact that the laboratory personnel did not detect the mating of the animals. The lack of inclusion of non-confirmed mated females who were pregnant and the use of multiple matings to different animals both raise questions on the calculations used to prepare the mating and fertility indices.

EPA, as the sponsoring authority for NMP at the Organization of Economic Development and Cooperation (OECD) Screening Information Dataset (SIDS) Initial Assessment Meeting, should be well aware that the international regulatory authorities rated the Exxon study (reliability score of 2) inferior in quality to those conducted by the NMP Producers Group (reliability scores of 1) (OECD 2007).

Finally, EPA's position that the fertility/fecundity effects in the Exxon study are purportedly "biologically significant" is not supported by the two additional two-generation reproductive toxicity studies sponsored by the NMP Producers Group, which had the higher

---

[4] In the 500 mg/kg/day group, there were only 13 litters, and therefore only 26 male and 26 female rats in this group were available for selection to populate the P2 (F1b) parents, even though the protocol called for 30 each.

ED_006308_00000213-00018

quality ranking score, nor is it supported by the other studies cited by EPA as providing such support (Sitarek *et al.* 2012 and Sitarek and Stetkiewicz 2008).

EPA Assumptions on Fertility Effects as a Chronic Toxicity End Point Are Problematic

Nothwithstanding the problems with the Exxon 1991 study, EPA's decision to rely on fertility effects with assumed early-life susceptibility in its 2019 risk assessment is problematic for the following reasons, which are further detailed in the appended Summit report:

Physiologically Based Pharmacokinetic (PBPK)-Derived Internal Dose -- EPA did not adequately consider rat size and associated internal dose within the context of its assumption of early-life susceptibility, which results in a nearly two-fold increase in the estimated NMP potency.

- *Window of Susceptibility* -- The duration effect pattern on reported reproductive effects from the benchmark dose (BMD) modeling results contradicts the EPA assumption of early-life susceptibility. Without any specific evidence supporting a window of susceptibility analysis, it is typical to assume that any effects observed reflect the cumulative exposure to NMP.

- *Applicability to Worker Exposures* -- An assumption of early-life susceptibility for this end point is inconsistent with the exposure scenarios to which the assessment is applied. Because worker exposure scenarios to NMP are for exposures to adult workers, end points that are assumed to be pertinent to early-life exposures are not considered applicable.

- *Underestimation of NMP Dose* -- The Exxon 1991 report failed to adjust the concentrations of NMP in feed to reflect changes in food consumption that occur during pregnancy and lactation. This oversight resulted in the doses of NMP being significantly elevated during the period of lactation (*e.g.*, dose rates during week 3 of lactation were two- to three-fold higher than during week 1 of lactation), which are of primary importance in EPA's assumption of early-life susceptibility.

- *Consideration of Other Reproductive Toxicity Studies* -- As noted in the Summit report, for other end points (acute effects on developmental toxicity; chronic effects on fetal/pup bw changes), EPA appropriately relied on the results of multiple studies (*i.e.*, combining data sets for oral, inhalation, and dermal exposures to NMP to examine overall patterns).

ED_006308_00000213-00019

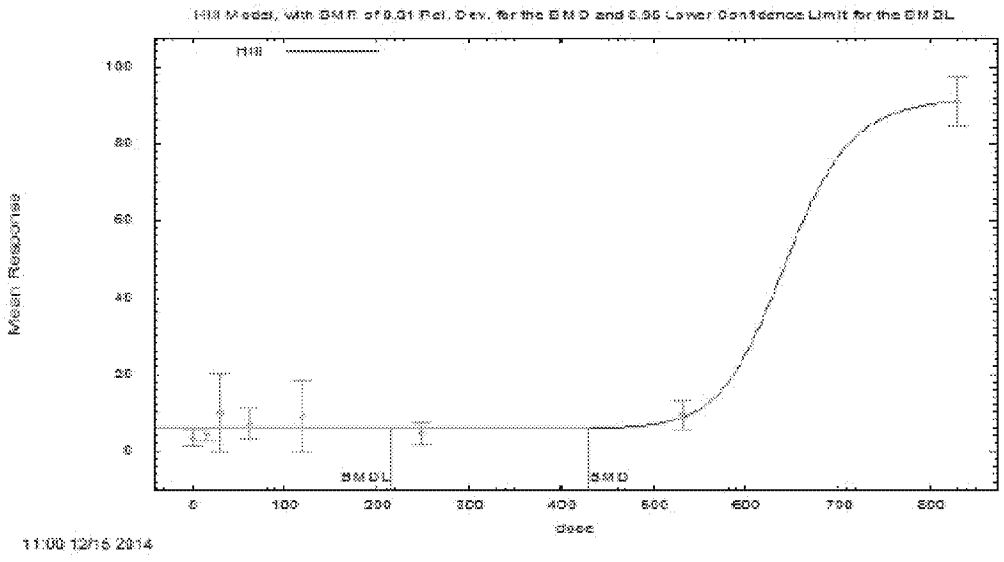
The results of the two follow-up studies conducted by the NMP Producers Group, showing that effects on fertility and fecundity were not observed in rats exposed to dietary 50-500 mg/kg/day NMP when feed levels were appropriately adjusted for changes in food consumption (NMP Producers Group 1999a, 1999b), suggest that the design flaw noted above for Exxon 1991 may be of critical importance to the manifestation of the effects observed in rats exposed to the same dose range. For the sake of consistency and completeness, we recommend that EPA consider all the fertility and fecundity data, not within the context of each other, but within an overall data quality context, which would place the Exxon 1991 study at a lower quality level than other reproductive toxicity studies, including those for dietary exposure (NMP Producers Group 1999a, 1999b) and inhalation exposure (Solomon *et al.* 1995).

EPA Benchmark Response Rate of 1% for Acute Toxicity End Point Is Inappropriate

As detailed in the appended Summit report, EPA's adoption of a benchmark response rate (BMR) of 1% relative deviation in determining its point of departure (POD) ($BMDL_{1RD}$) value for fetal resorptions (Table 3-3-2 of EPA *Benchmark Dose Modeling Supplemental File* (EPA 2019b)) is not supported by the data for NMP, is inconsistent with standard practice and EPA guidelines, and should not be used.

In addition to the discussions in the Summit report, the NMP Producers Group notes additional points that show the BMR rate of 1% is inappropriate:

- The figure below from *Benchmark Dose Modeling Supplemental File* (EPA 2019b) shows that even if one ignores the fact that the goodness of fit for all EPA model runs of the combined data is *unacceptable* per EPA BMD guidelines (*i.e.*, <0.0001 when it should be >0.1), a conservative BMR of 0.5 standard deviations (SD) more than doubles the benchmark dose level (BMDL) (*i.e.*, from 216 to 514).



- In Table 3-3-2 from Section 3.1 of the draft assessment report (EPA 2019a) (provided below), EPA acknowledges that none of the models had an acceptable p-value of >0.1. EPA also inexplicably indicates that the visual fit from the Hill model, with a p-value of <0.0001, was acceptable.

3.1 Results for Saillenfait et al., 2002 and 2003 combined using C_{max}

Table 3-3-2 Model Predictions for Resorptions in Rats Exposed to NMP via Gavage or Inhalation Using C_{max} as the Dose Metric (Saillenfait et al. (2003; 2002))
BMR = 1% Relative Deviation (RD) and for Comparison 0.5 and 1 Standard Deviation (SD)

Model[a]	Goodness of fit		BMD_{1SD} (mg/L)	$BMDL_{1SD}$ (mg/L)	$BMD_{0.5SD}$ (mg/L)	$BMDL_{0.5SD}$ (mg/L)	BMD_{1RD} (mg/L)	$BMDL_{1RD}$ (mg/L)	Basis for model selection
	p-value	AIC							
Exponential (M2)	<0.0001	1288.45	1.60	1.26	424	349	530	468	While none of the models had an acceptable p-value (>0.1) the visual fit appears adequate, the lowest AIC, the Hill model was selected.
Exponential (M3)	<0.0001	1263.09	247	97.9	621	510	685	602	
Exponential (M4)	<0.0001	1364.53	0.122	0.0122	58.2	44.5	116	89.1	
Exponential (M5)	<0.0001	1265.04	326	215	593	514	648	583	
Hill	**<0.0001**	**1263.03**	429	216	558	514	582	548	
Power	<0.0001	1263.04	326	215	593	514	648	583	
Polynomial 4°	<0.0001	1276.48	128	77.6	436	419	518	504	
Polynomial 3°	<0.0001	1300.17	66.7	55.2	359	345	452	435	
Polynomial 2°	<0.0001	1336.49	19.3	3.77	247	215	349	317	
Linear	<0.0001	1362.53	0.121	0.0122	58.2	44.5	116	89.1	

Notes:
[a] Modeled variance case presented (BMDS Test 2 p-value = <0.0001), selected model in bold; scaled residuals for selected model for doses 0, 15.01, 30.34, 61.86, 120, 250, 531 and 831 mg/L were -1.42, -0.619, 1.41, 0.401, 1.1, -0.599, 0.29 and -0.00443, respectively.

ED_006308_00000213-00021

To further evaluate the BMR issue, Summit Toxicology conducted supplemental benchmark dose analyses for the acute toxicity of NMP. As outlined in the appended Summit report, the supplemental analyses included the critical consideration that inhalation doses to rats may be underestimated by the PBPK model, as well as issues identified during the SACC review for NMP.

The Summit supplemental analyses used dichotomous data, which were not considered by EPA, a conservative BMR of 5% and the current BMD software to calculate a BMDL (517 mg/L). This BMDL is essentially the same as that calculated by EPA (514 mg/L) using continuous data, a conservative BMR of 0.5 SD, and an older version of BMDS (Benchmark Dose Software). Unlike EPA's modeling at a BMR of 1%, however, the Summit modeling with a 5% BMR results in an acceptable model fit (p-value of 0.216 vs. <0.0001).

Given the issues noted above and the unfounded precedent that would be set with a 1% BMR, EPA must adopt a BMR of 0.5 SD.

As further detailed in Appendix 1, the Summit analyses showed that software version differences between BMDS 2.5 and 3.1.2 appear to have an impact on the results. For example, EPA's assessment using version 2.5 relied upon an assumption that variance is not constant across dose groups, whereas in version 3.1.2, this option failed to return BMD results. In addition, the p-value (<0.0001 vs. 0.216) for BMDS runs using the latest software version appear to improve compared to the version used by EPA. The NMP Producers Group recommends that EPA rely on the latest version in the final assessment.

Given the issues noted above, the unfounded precedent that would be set with a 1% BMR, and the outcome of the Summit analyses, we urge EPA to adopt a BMR of 0.5 SD in the final risk assessment.

Acute Point of Departure Value Should Be Adjusted Higher

The appended Summit Toxicology report reviews the relative importance of using NMP-specific data in assessing single-day exposures. Summit concludes that EPA's acute POD value of 214 mg/L based on 15-day exposures should be adjusted to a value that is 2.3-fold higher (492 mg/L) for a single-day exposure.

Dose-Response Assessment (Section 3.2.5 of the Draft Risk Evaluation)

PBPK-Derived Internal Doses for Rats after Inhalation Exposures Are Underestimated

EPA's acute toxicity assessment for fetal resorptions (as well as chronic toxicity assessment for fetal bw changes) in rats considers only the inhalation of NMP vapor under the conditions of the whole-body inhalation toxicity studies. In contrast, a fuller characterization of exposure pathways should be conducted for whole-body exposures to humans (*i.e.*, dermal exposure to NMP vapor is explicitly included). In both the 2015 and 2019 assessments, EPA acknowledges that dermal absorption of NMP vapors in the whole-body inhalation studies likely contributed to the toxicity; yet EPA did not incorporate this contribution in the model. The concerns noted below related to model predictions for whole-body exposures for developmental toxicity studies that do not include contributions from dermal uptake of vapors or oral uptake via grooming are addressed fully in the appended Summit report.

- There is clear evidence that the dermal vapor pathway is important in humans where the combined contributions from inhalation and dermal absorption of vapor (when wearing trousers and short-sleeved shirts) to the internal dose were 1.5- (during moderate workload) to 1.7-fold (while at rest) higher than that from inhalation alone (Bader *et al.* 2008).

- Because rat skin is 2- to 3-fold more permeable to dermally applied NMP than human skin (EPA 2019a), whole-body exposure of resting rats to NMP vapor is expected to result in an internal dose that is 3- to 5-fold higher than that after nose-only exposure (*i.e.*, 1.7-fold × 2 or 3).

- Because of grooming behavior in rats, the oral dose received from fur is expected to be considerably higher than the incidental ingestion of vapors in humans.

The original PBPK model developer, Poet *et al.* 2016, estimates that if contributions from these two pathways during whole-body exposures increased the total NMP dose by a factor of 3.3-fold over that from vapor inhalation alone, the apparent discrepancy in NMP potency observed following inhalation vs. oral exposures for fetal bw changes would be resolved (*i.e.*, concordance across route of exposure). As discussed above, a factor of 3.3-fold is reasonable and consistent with available data. EPA should incorporate consideration of this important issue in the final risk assessment.

Parameter Values Used in EPA's PBPK Model Are Overly Conservative

Parameterization of the human PBPK model differed between the 2015 EPA Risk Assessment and Poet *et al.* (2016), particularly with the selective treatment of the Bader *et al.* (2008) study by EPA. Specifically, EPA's reliance on only the low-concentration (10 mg/m^3) data of Bader *et al.* (2008) (ignoring data collected for 40 and 80 mg/m^3) results in an overestimation of potential hazard for the high concentration exposures simulated in EPA's assessment (many scenarios with peaks exceeding 80 mg/m^3). As further detailed in the appended Summit report, this decision to rely solely on the low concentration impacts multiple mid- and high-exposure scenarios. Given that conditions of use with anticipated high concentrations of NMP in air will be a driving factor in EPA's final assessment, EPA must appropriately parameterize the PBPK model, as recommended by Summit.

Risk Characterization (Section 4 of the Draft Risk Evaluation)

MOE for Workers Is Overly Conservative

The MOE for workers should be 20 for acute exposures and 21 for chronic. In the 2019 draft Risk Assessment, EPA identified an MOE of 30 derived from default values of 10 for intraspecies variability among humans (UF_H) and 3 for interspecies variability between animals and humans (UH_A). The default value of 10 for UF_H assumes equivalent contributions of 3.16 ($10^{0.5}$) for its toxicokinetic (tk) and toxicodynamic (td) components. As outlined in the following paragraph, EPA should not be relying on a default value for UF_H tk and instead should use the PBPK modeling of human data from Bader and van Thriel (2006).

Based on PBPK modeling of individual data from human volunteers exposed via inhalation (which reflects uptake via inhalation and dermal absorption of vapor) to three concentrations of NMP vapor (Bader and van Thriel 2006), peak NMP levels in blood (mg/L) for each exposure concentration were determined to have a coefficient of variation (CV) of approximately 0.21, while AUC blood levels (mg/L × h) for each exposure concentration had a CV of approximately 0.28 (Poet *et al.* 2016). This information should be used to replace the default value for UF_H tk with a data-derived extrapolation factor (DDEF) (EPA 2011). Using the CV for peak blood levels and assuming a normal distribution in a healthy worker population, a tk DDEF of 2.0 (1.21 × 1.645, rounded to two significant figures) is judged sufficient to protect 95% of a healthy worker population and yields a net UF_H of 6.3 [2.1 (tk) × 3.16 (td)]. Using the CV for AUC data similarly, a DDEF of 2.1 (1.28 × 1.645) and a net UF_H of 6.6 [2.0 (tk) × 3.16 (td)] can be calculated. When these net UF_H values are combined with the UF_A value of 3.16, the composite uncertainty factors for acute (peak) and chronic (AUC) exposures to workers are 20 (6.3 × 3.16) and 21 (6.6 × 3.16), respectively.

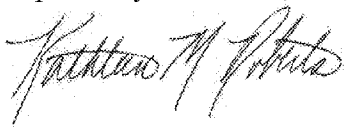
ED_006308_00000213-00024

EPA Should Re-Evaluate Scenarios with Unreasonable Risk Conclusions

Assuming that EPA makes the scientifically justified corrections outlined in these comments, many, if not all of the scenarios in which EPA concluded unreasonable risk will show that adequate protections exist.

The NMP Producers Group appreciates the opportunity to provide these comments. We remain committed to working with EPA on the issues outlined in this letter, including but not limited to addressing the urgent need to protect property value of sponsored study reports under TSCA.

Respectfully submitted,



Kathleen M. Roberts
Manager
NMP Producers Group

Reference List

Abt Associates. 1992. Methylene chloride consumer products use survey findings. OMB 3041-0098. Prepared by Abt Associates, Inc., for the U.S. Consumer Product Safety Commission, Bethesda, MD.

Bader, M., Van Thriel, C. 2006. Human volunteer study on biomarkers of N-methyl-2-pyrrolidone (NMP) after inhalation exposure. Hannover and Dortmund, Germany: Hannover Medical School and University of Dortmund, Institute of Occupational Physiology.

Bader, M., Wrbitzky, R., Blaszkewicz, M., Schäper, M., van Thriel, C. 2008. Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch. Toxicol. 82(1), 13-20.

Crook, V., Simpson, A. 2007. Protective glove selection for workers using NMP containing products - Graffiti removal. Health & Safety Laboratory, unpublished report. HSL/2007/41. http://www.hse.gov.uk/research/hsl_pdf/2007/hsl0741.pdf.

Exxon Biomedical Sciences. 1991. Multigeneration rat reproduction study with N-methylpyrrolidone. Project No. 236535, Nov. 26. Wayne, NJ: GAF Corp.

Faber, W.D. 2020. Comparison of fertility and fecundity results from three two-generation reproductive toxicity studies evaluating N-methyl-2-pyrrolidone. Lyondell Chemical Company report.

Kirman, C.R. 2020. Using PBPK modeling to assess the efficacy of glove materials in reducing internal doses and potential hazards of N-methylpyrrolidone during paint stripping. Submitted to the Journal for Exposure Science and Environmental Epidemiology (publication pending).

NMP Producers Group. 1999a. Two generation reproduction toxicity study with N-methylpyrrolidone (NMP) in Sprague-Dawley rats: Administration in the diet. (Project No. 97-4106). East Millstone, NJ: Huntingdon Life Sciences, unpublished report.

NMP Producers Group. 1999b. Two generation reproduction toxicity study with N-methylpyrrolidone (NMP) in Wistar rats: Administration in the diet. (Project No. 70R0056/97008). Ludwigshafen, Germany: Department of Toxicology of BASF Aktiengesellschaft.

OECD. 2007. SIDS initial assessment report on 1-methyl-2-pyrrolidone. Washington, DC: Organization for Economic Cooperation and Development.

Poet, T.S., Schlosser, P.M., Rodriguez, C.E., Parod, R.J., Rodwell, D.E., Kirman, C.R. 2016. Using physiologically based pharmacokinetic modeling and benchmark dose methods to derive an occupational exposure limit for N-methylpyrrolidone. Regul. Toxicol. Pharmacol. Apr., 76, 102-112. doi: 10.1016/j.yrtph.2015.12.020.

Saillenfait, A.M., Gallissot, F., Morel, G. 2003. Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure. Food Chem. Toxicol. 41(4), 583-588.

Saillenfait, A. M., Gallissot, F., Langonne, I., Sabate, J. P. 2002. Developmental Toxicity of N-Methyl-2-Pyrrolidone Administered Orally to Rats. Food Chem. Toxicol. 40(11), 1705-1712.

Sitarek, K., Stetkiewicz, J. 2008. Assessment of reproductive toxicity and gonadotoxic potential of N-methyl-2-pyrrolidone in male rats. Int. J. Occup. Med. Environ. Health 21(1), 73-80. doi: 10.2478/v10001-008-0006-z.

Sitarek, K., Stetkiewicz, J., Wąsowicz, W. 2012. Evaluation of reproductive disorders in female rats exposed to N-methyl-2-pyrrolidone. Birth Defects Res. B Dev. Reprod. Toxicol. 95(3), 195-201. doi: 10.1002/bdrb.21001.

Solomon, H.M., Burgess, B.A.; Kennedy, G.L., Jr., Staples, R.E. 1995. 1-Methyl-2-pyrrolidone (NMP): Reproductive and developmental toxicity study by inhalation in the rat. Drug Chem. Toxicol. 18(4), 271-293. doi: 10.3109/01480549509014324.

Stull, J.O., Thomas, R.W., James, L.E. 2002. A comparative analysis of glove permeation resistance to paint stripping formulations. AIHA J. (Fairfax, Va.) 63(1), 62-71.

U.S. EPA. 2011. Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation. EPA/100/J-11/001. Washington, DC: U.S. EPA.

U.S. EPA. 2015. TSCA work plan chemical risk assessment. N-Methylpyrrolidone: Paint stripper use. In Office of Chemical Safety and Pollution Prevention. (740-R1-5002). Washington, DC: U.S. EPA. https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment-n.

U.S. EPA. 2019a. Draft risk evaluation for N-methylpyrrolidone (2-pyrrolidinone, 1-methyl-). Washington, DC: U.S. EPA.

U.S. EPA. 2019b. Draft risk evaluation for N-methylpyrrolidone (2-pyrrolidinone, 1-methyl-), Benchmark dose modeling supplemental file. Peer review draft. Washington, DC: U.S. EPA.

Zellers, E.T., Sulewski, R. 1993. Modeling the temperature dependence of N-methylpyrrolidone permeation through butyl- and natural-rubber gloves. Am. Ind. Hyg. Assoc. J. 54(9), 465-479.

Appendix 1 -- Summit Toxicology Report

Critical Review of USEPA's Draft Risk Evaluation for N-Methylpyrrolidone

January 20, 2019

Prepared for:

The NMP Producer's Group

Prepared by:

SUMMIT TOXICOLOGY

Summit Toxicology has been retained by the NMP Producers Group to review and comment on USEPA's draft report entitled, *Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP) CASRN: 872-50-4* and its supplemental files (USEPA, 2019). USEPA's report summarizes a large and complex risk assessment, and reflects a significant level of effort by USEPA, conducted under an aggressive timeline as dictated by TSCA regulations. We compliment USEPA for getting the draft assessment to this point, and applaud their use of the following methods and tools that represent the best available science:

- *Physiologically Based Pharmacokinetic (PBPK) Modeling* - By incorporating PBPK modeling into the risk assessment, USEPA has ensured that: (1) important species differences in NMP metabolism between rats and humans are addressed, thereby reducing uncertainty in the assessment; (2) internal doses resulting from exposures to NMP via different routes (primarily inhalation and dermal) can be aggregated together, thereby eliminating the need for route-specific toxicity values. USEPA's recent uploading of the PBPK model files to make them publicly available is greatly appreciated.
- *Benchmark Dose (BMD) Modeling* – By utilizing BMD modeling, USEPA helps ensure that the assessment for NMP: (1) accounts for all of the dose-response data from the selected reproductive and developmental toxicity studies; (2) increases consistency in the point of departure; and (3) accounts for statistical uncertainties in the underlying data. Furthermore, by combining dose-response data across studies (e.g., the oral and inhalation study data of Saillenfait et al. (2002, 2003) for developmental effects), USEPA has provided a more complete characterization of the dose-response relationship than would be possible if each study were assessed separately.

While EPA is to be commended for utilizing the best available science by using PBPK and BMD modeling in this risk assessment, there are other areas where USEPA has not relied upon the best available science. Specific recommendations for improving the assessment are summarized below.

1. Need for Better Incorporation of NMP-Specific Data to Replace Assumptions

Risk assessments typically incorporate a mixture of science/data, policy, and assumptions to support risk-based decisions. Although USEPA's incorporation of best available science in some instances is recognized, there are multiple instances in the risk assessment where assumptions were made by USEPA without the benefit of considering NMP-specific data. These instances are listed in **Table 1**, and are discussed in the remainder of this section.

Table 1. Summary of Instances Where NMP-Specific Data Can Be Used to Replace Assumptions in USEPA's TSCA Risk Assessment

Risk Assessment Component	Issue	Assumption Adopted in USEPA's Draft Risk Assessment	Position Supported by NMP-Specific Data	For Details, See Section:

ED_006308_00000213-00030

Exposure Assessment	Glove protection factors (PFs)	Default PF values of 5, 10, and 20 were adopted	Measurements of NMP permeation indicate a much wider range of PF values (1.1- to 1,900; Kirman, 2020; Attachment 1)	1.1
	Air saturation concentration (Csat)	Csat value of 1,013 mg/m^3 is cited in the text, but a value of 1,800 mg/m^3 is noted in supplemental files	Measured data for NMP indicate Csat is highly dependent upon air humidity (OECD, 2007), and under most conditions will be much lower than assumed	1.2
Acute Toxicity	Benchmark response rate (BMR)	A BMR of 1% is adopted	BMD modeling of the incidence data from the key study for NMP (Saillenfait et al., 2002, 2003) indicates a BMR of 5% incidence (considered default value for developmental endpoints) is equivalent to use of 0.5SD for continuous data	1.3
	Exposure duration concordance	1-day and 15-day gestational exposures are assumed to be equivalent	Measured data for fetal resorptions in mice exposed to NMP indicate the difference between these two durations is approximately 2-fold (Schmidt, 1976)	1.4
Chronic Toxicity	Endpoint selection/data	Assessment relies on the results from a single reproductive toxicity study (Exxon, 1991) for establishing POD	Multiple follow-up reproductive studies have been conducted for NMP (Thornton, 1999; Hellwig and Hildebrand, 1999; Solomon et al., 1995), providing a weight-of-evidence that counters the results of Exxon (1991)	1.5
	Early life susceptibility	In adopting internal doses for a young (50 g) rat for BMD modeling, USEPA assumes reproductive toxicity effects are attributable to early life susceptibility	NMP data from Exxon (1991) are consistent with a duration effect, rather than early-life susceptibility, for the critical endpoints	1.6
PBPK Modeling	Human metabolism parameterization	Human metabolism parameters were optimized to low concentration (2.5 ppm) TK data only (Bader and van Thriel, 2006)	TK data collected in human at higher concentrations (10 and 20 ppm; Bader and van Thriel, 2006) are more relevant to the high-end exposures i.e., >2.5 ppm, in some cases exceeding this level by orders of magnitude) characterized in the risk assessment (Bader and van Thriel, 2006)	1.7
	Rat inhalation underestimation	Nose-only exposures were used to estimate NMP uptake in the PBPK model	Measured data in humans indicates dermal absorption of NMP vapor is significant (Bader	1.8

ED_006308_00000213-00031

		for rat whole-body inhalation exposures	et al., 2008). Measured data in rats indicate dermal absorption of NMP aerosols from air following whole-body exposures is significant (BASF, unpublished report)	

1.1 PBPK-Derived Glove Protection Factors for NMP

In the draft risk assessment, assumptions were made for glove protection factor (PF) values of 5, 10, and 20 that were then applied to adjust exposed skin surface area to liquid NMP (i.e., effective surface area was reduced 5-, 10-, or 20-fold). These values represent default values as defined in the ECETOC TRA v3 model (Marquart et al., 2017), and do not reflect available measurements for the permeation of NMP through glove materials, which is well studied. Three independent studies have been conducted, which demonstrate that the degree of NMP permeation can vary by several orders of magnitude depending upon the material used and NMP product formulation (Stull et al., 2002; Crook and Simpson, 2007; Zellers and Sulewski, 1993). These data have been used to derive chemical-specific glove protection factors (Kirman, 2020; Attachment 1), as summarized in **Table 2**.

Table 2. NMP-Specific Data Used to Derive NMP Glove Protection Factors for Different Glove Materials (Kirman, 2020; Attachment 1)

Liquid NMP Exposure	Glove Category[1]	Protection Factors for Specific Internal Dose Measures[2]	
		Cmax	AUC
NMP Solution	Minimal Protection	1.3 (1.1-18)	1.3 (1.1-18)
	Moderate Protection	4.7 (3.5-8.4)	4.9 (3.6-8.7)
	Maximal Protection	68 (12-180)	71 (12-190)
Neat NMP	Minimal Protection	2.5 (1.3-130)	3.0 (1.4-180)
	Moderate Protection	28 (18-56)	39 (26-78)
	Maximal Protection	510 (83-1400)	720 (120-1900)

[1]Minimal protection = natural rubber, nitrile, latex; Moderate protection = polyethylene; Maximal protection = butyl, laminate
[2]Values reflect the mean for the glove category, with the range of values indicated in parentheses (Kirman, 2020; Attachment 1).

The results obtained from PBPK modeling using NMP-specific data indicate that the impact of gloves on NMP dose and risk is much more variable than characterized by USEPA, and is not adequately characterized by the default range of PF values of 5-20. On the one hand, a default PF of 5 appears too high for some glove materials (i.e., those in the minimal protection category), while on the other hand a default PF value of 20 appears too low for other glove materials (i.e., those in the maximal protection category).

- ***Recommendation - We recommend that USEPA incorporate NMP-specific data on glove permeation into its risk assessment to provide a more accurate characterization of their impact on internal dose and risk.***

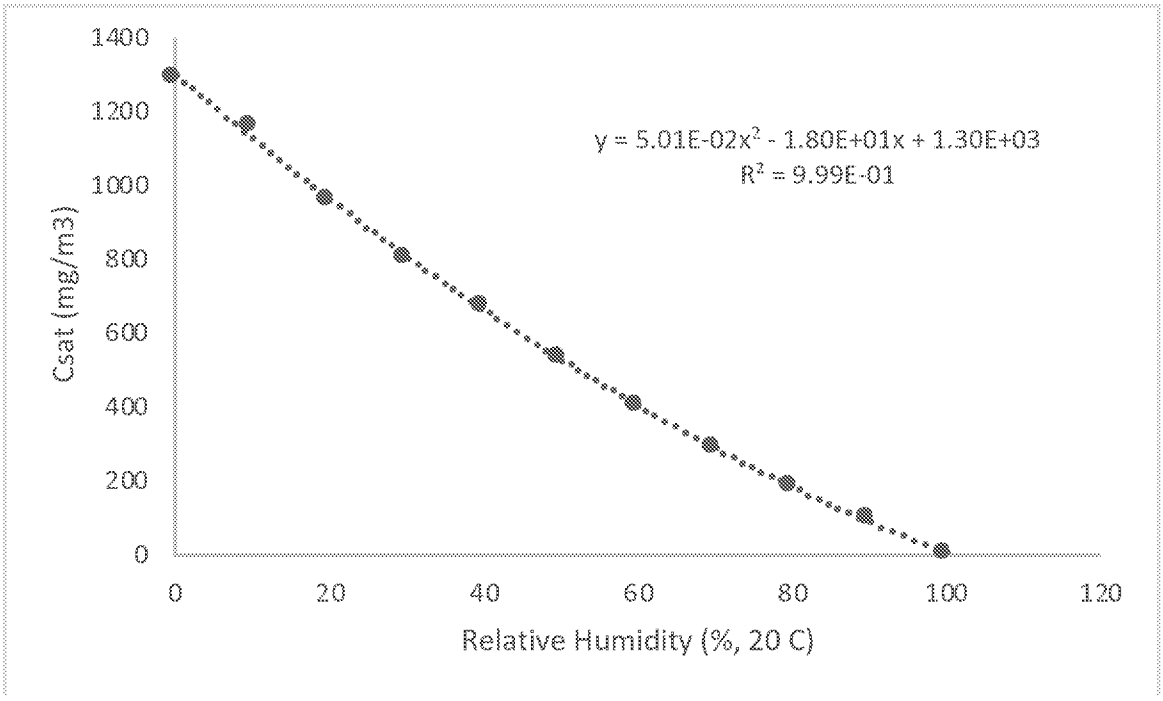
ED_006308_00000213-00032

1.2 Air Saturation

In modeling indoor air concentrations for NMP, USEPA's draft risk assessment adopts a value for the saturation of NMP vapor in air. However, it is unclear what value was adopted, since in the text a value of 1,013 mg/m^3 is cited (e.g., Table 6-3 of USEPA, 2019), while some modeled concentrations appear to reach peak concentrations of 1,300 mg/m^3, and supplemental material indicate a value of 1,840 mg/m^3 was used in the air modeling. Regardless, the value of Csat used in the indoor air modeling for NMP appears to be very conservative.

The saturation concentration for NMP in air is humidity-dependent, with a relationship that is nearly linear (**Figure 1**; OECD, 2007).

Figure 1. NMP-Specific Data on Air Saturation (Csat) vs. Relative Humidity (OECD, 2007)



Based upon this relationship, Csat values of 1,013 and 1,840 mg/m^3 correspond to relative humidity values of approximately 15% and null (outside the observation range under the test conditions), respectively. Furthermore, these values also far exceed those that can be reliably maintained under controlled laboratory conditions (approximately 120 ppm (486 mg/m^3) for toxicity testing) (Solomon et al., 1995; Saillenfait et al., 2003). In USEPA's study of consumer exposure to NMP in paint strippers (USEPA, 1994), researchers noted a "sink effect" for NMP and other semi-volatile chemicals due to the adsorption to test chamber surfaces at aerosol concentrations of up to approximately 74 ppm (300 mg/m^3).

Data are available for humidity in residential buildings by climate region (e.g., USHUD, 2010), which indicate that average relative humidity in indoor is typically near 50% (means ranging

ED_006308_00000213-00033

from 47.9-53.1%), which exhibits both temporal and regional variation. A relative humidity of 50% would correspond to a Csat value of approximately 525 mg/m^3, which is considerably lower than the value assumed by USEPA.

- ***Recommendation - Based upon this information, we have the following recommendations:***
  1. ***The distribution of relative humidity in indoor air in the United States (e.g., low, average, and high humidity values of ~15%, ~50%, and ~85%) should be characterized based on recent surveys (e.g., USHUD, 2010) and incorporated into the risk assessment to characterize a distribution of Csat values based on the relationship described in Figure 1 (e.g., 1030, 525, and 132 mg/m^3) for indoor air modeling.***
  2. ***Given the relative vapor pressures of NMP and water, application of aqueous NMP products is expected to increase the relative humidity of indoor air, particularly under assumptions of low ventilation. For this reason, separate assumptions for relative humidity should be made for the use of aqueous vs. non-aqueous NMP products, to avoid an unrealistic assumption of low humidity following application of aqueous NMP products.***

1.3 Acute Benchmark Response Rate

Embedded in USEPA's BMD analysis for acute endpoints is a precedent setting decision that is not supported by the data for NMP, and is inconsistent with standard practice and USEPA guidelines (USEPA, 2012). Specifically, USEPA adopted a benchmark response rate of 1% relative deviation in determining its point of departure (BMDL1RD) value for fetal resorptions (Table 3-3-2 of USEPA Benchmark Dose Modeling Supplemental File). This value is inappropriate for a number of reasons:

- *Inconsistent with NMP Data* – A BMR of 1% is inconsistent with the incidence data of Saillenfait et al. (2002, 2003). Dose-response (dichotomous) data from the oral and inhalation developmental toxicity studies of Saillenfait et al. (2003, 2003), are presented in **Tables 3**. Dichotomous data for developmental toxicity studies are best assessed using a nested benchmark dose model to account for potential litter effects (i.e., effects that are not randomly distributed across litters), however, this would require access to the raw study data, which to date are not available.

Table 3. Saillenfait et al. (2002, 2003) Data Expressed as Dichotomous Data (i.e., fetal incidence)

			Fetal Resorption (fetal incidence basis)*	
Study	Dose or Conc (mg/kg-day or ppm)	Cmax (mg/L)	n	r

ED_006308_00000213-00034

Saillenfait et al. 2002 (oral)	0	0	279	11
	125	120	299	27
	250	250	319	14
	500	531	350	33
	750	831	345	314
Saillenfait et al. 2003 (inhalation)	0	0	343	9
	30	15.01	268	12
	60	30.34	282	28
	120	61.86	323	23

*Calculated from summary information (number of litters, mean values for litter size and resorption rates per litter provided in the publication), rounded to the nearest whole number.

A BMR of 5% is well established for determining the point of departure for the incidence of developmental toxicity endpoints. Using the incidence data for NMP in **Table 3**, the BMDL05 was determined to be 517 mg/L (log-probit model), which is essentially identical to that estimated by USEPA for the BMD0.5SD (514 mg/L; Table 3-3-2 of USEPA's Benchmark Dose Supplemental File) for continuous data by USEPA (i.e., BMR of 0.5SD for continuous data is equivalent to a BMR of 5% for incidence data).

In addition, when a BMR value is set too low, it results in extrapolation of the dose-response models below the range of observation defined by the data, where competing models can differ widely in their predictions for the POD. For the NMP data modeled by USEPA, the range of BMDL1RD values defined by the different continuous models spans a range of more than 4 orders of magnitude. In comparison, ranges defined by the different continuous models for higher BMR values (BMDL0.5SD and BMDL1SD) are in much better agreement, with ranges of approximately 1 order of magnitude and less than 1 order of magnitude, respectively.

- *Inconsistent with Standard Practice* – A survey of the IRIS database reveals 30 assessments in which BMD methods have been applied to continuous data (**Table 4**). A majority of these assessments (18/30) have relied upon 1SD as the BMR, with a minority relying upon relative deviations of 10% (6/30) or 5% (5/30). In no cases (0/30) was a relative deviation of 1% adopted in a previous IRIS assessment. When the assessments are narrowed to examine only those based on a developmental endpoint (n=7), 4 assessments were based on a BMR of 1SD, and 3 assessments were based on a BMR of 5%. Because IRIS values are used to help prioritize chemical risk issues across chemicals, the arbitrary use of a lower BMR value for NMP serves to distort any such comparisons that include NMP.

Table 4. Summary of BMR Values Used in BMD Modeling of Continuous Data Sets in USEPA's IRIS Database

ED_006308_00000213-00035

Endpoint	Chemical	Tox Value	BMR	Endpoint	Date
Developmental	Methylmercury	Oral RfD	5%	Developmental neuropsychological impairment	7/27/01
	Cyclohexane	Inhalation RfC	1SD	pup BW	9/11/03
	Methyl ethyl ketone	Oral RfD	5%	pup BW	9/26/03
	Boron	Oral RfD	5%	fetal weight	8/5/04
	Methanol	Inhalation RfC	1SD	brain weight in rat pups	9/30/13
	Tetrahydrofuran	Oral RfD	1SD	decreased pup bw gain	2/21/12
	Benzo(a)pyrene	Oral RfD	1SD	Developmental neurobehavioral effects	1/19/17
Other	Carbon disulfide	Inhalation RfC	10%	peripheral nerve dysfunction	8/1/95
	Tributyltin oxide	Oral RfD	10%	immunosuppression	9/1/97
	Ethylene glycol monobutyl ether	Oral RfD	5%	mean cell volume	12/30/99
	Phenol	Oral RfD	1SD	maternal BW	9/30/02
	Benzene	Oral RfD	1SD	lymphocyte count	4/17/03
	Toluene	Oral RfD	1SD	kidney weight	9/23/05
	n-Hexane	Inhalation RfC	1SD	peripheral nerve dysfunction	12/23/05
	Trichloroethane	Oral RfD	10%	BW	9/28/07
	Pentabromodiphenylether	Oral RfD	1SD	neurobehavioral effects	6/30/08
	Tetrabromodiphenylether	Oral RfD	1SD	neurobehavioral effects	6/30/08
	Nitrobenzene	Oral RfD	1SD	methemoglobin levels	2/6/09
	Carbon tetrachloride	Oral RfD	2XMean	Serum SDH	3/31/10
	cis-1-2-Dichloroethylene	Oral RfD	10%	Kidney weight	9/30/10
	trans-1,2-Dichloroethylene	Oral RfD	1SD	immune response	9/30/10
	2-Hexanone	Inhalation RfC	5%	nerve conduction velocity	9/25/09
	Hydrogen cyanide	Oral RfD	1SD	epididymis weight	9/28/10
	1,1,2,2-Tetrachloroethane	Oral RfD	1SD	liver weight	9/30/10
	Tetrahydrofuran	Inhalation RfC	10%	liver weight	2/21/12
	1,2,3-Trichloropropane	Oral RfD	10%	liver weight	9/30/09
	1,2,4 Trimethylbenzene	Oral RfC	1SD	Neurological	9/9/16
	1,2,4 Trimethylbenzene	Inhalation RfC	1SD	Neurological	9/9/16
	1,3,5-Trimethylbenzene	Oral RfC	1SD	Neurological	9/9/16
	1,3,5-Trimethylbenzene	Inhalation RfC	1SD	Neurological	9/9/16

- *Inconsistent with USEPA Guidelines* – There is no basis for adopting a BMR of 1% relative deviation as a level that is "*generally considered to be biologically significant*". It is recognized that fetal resorptions reflect a severe effect. However,

this does not justify the specific adoption of a BMR of 1%. For example, cancer is also considered to be a severe effect, and yet nearly all cancer slope factors derived by USEPA are based on a BMR of 10% (incidence basis). Moreover, USEPA BMD guidelines explicitly address the potential issue of endpoint severity in stating that *"for frank effects, a lower BMR may be warranted (e.g., 0.5SD)"* when modeling continuous data (USEPA, 2012).

- ***Recommendation – We recommend that USEPA adopt a BMR of 0.5SD instead of 1% for fetal resorptions assessed as continuous data in their acute dose-response assessment for NMP.***

1.4 Acute Exposure Duration Concordance

USEPA's toxicity value for acute exposures is based upon studies that included a 15-day exposure period during gestation (GD6-20; Saillenfait et al., 2002, 2003). In contrast, USEPA's exposure assessment included a 1-day exposure assumption for acute consumer and worker scenarios. USEPA's default assumption that developmental effects could arise as a result of a single exposure (i.e., duration equivalence of 15-day and 1-day exposures) is a conservative one. The relationship between acute (single) exposures and repeated exposures in producing developmental effects has been examined for chemicals in general (van Raiij et al., 2003). The study authors reported that for the 22 chemicals assessed for fetal resorptions, which serves as the key endpoint of concern for USEPA acute toxicity value, the acute doses producing effects were on average 2.1-fold higher than those associated with repeated doses. The results of this study would suggest that USEPA's 15-day POD value of 214 mg/L should be adjusted 2.1-fold higher (449 mg/L) for a single day exposure.

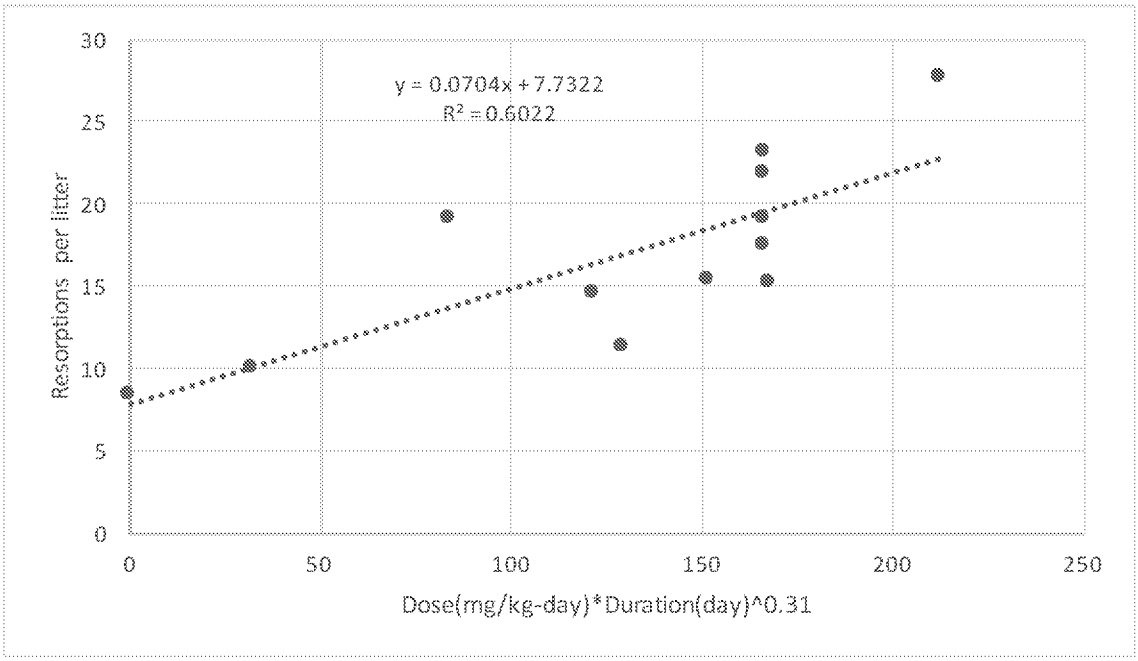
More importantly, there are NMP-specific data in the following study for which the issue of exposure duration can be addressed (Schmidt, 1976). The author conducted a study in mice that assessed the effect of multiple exposure periods for mice exposed to NMP via i.p. injection. This is an easy paper to miss (or dismiss) for acute toxicity value derivation since it is more than 40 years old, published in German (with an English translation), and involved non-physiological exposures to NMP (ip injection). However, it provides some very useful data for addressing the issue at hand. The exposure periods considered by the study authors included the following:

(1) 1-day exposures to 129 or 166 mg/kg NMP on days 3, 7, 9, or 11 of gestation;
(2) 5-day exposures to 74, 92, or 129 mg/kg-day NMP on days 7-11 of gestation; and
(3) 14-day exposures to 14, 37, or 74 mg/kg-day NMP on days 1-14 of gestation.

The authors of this study assessed fetal resorptions in control and treated groups (11 treatment variations of Dose x Time in total). Because this study included multiple durations and windows of exposure, these data permit an assessment of Haber's conjecture (equal values of $Dose \times Time^n$ produce equivalent responses). Schmidt (1976) resorption data assessed in terms of $Dose \times Time^n$ yield an optimized value for n of 0.31, as depicted in **Figure 2**.

ED_006308_00000213-00037

Figure 2. Use of Fetal Resorption Data for Mice Exposed to NMP (Schmidt, 1976) to Assess the Relative Importance of Dose and Exposure Duration



It should be noted that this evaluation for NMP assumes that a "day" is the appropriate time unit for scaling gestational exposures across species. To the extent that "fraction of gestation" serves as a more appropriate time unit for scaling, the recommendations in this comment may be viewed as conservative since a single day represents a much larger fraction of a rat's gestation period (1/20 days or 5%) than that of a human's gestation period (1/280 days or 0.4%).

- ***Recommendation – Based upon the relationship defined for the relative importance of dose and time using NMP-specific data, the NMP dose for a single day exposure is predicted to be approximately 2.3-fold higher than that for a 15-day exposure to yield an equivalent rate of fetal resorptions. The value supported by these data is remarkably similar to the average suggested by van Raiij et al. (2003) for chemicals as a group (2.3 vs. 2.1). Characterization of CxT relationships by USEPA has been used to support intra-day extrapolations under TSCA (e.g., methylene chloride risk assessment; USEPA, 2019b), and can readily be extended to address inter-day extrapolations as described above. Based upon this consideration, USEPA's acute POD value of 214 mg/L based 15-day exposures should be adjusted to a value that is 2.3-fold higher (492 mg/L) for a single day exposure.***

1.5 Chronic Endpoint Selection

For their chronic toxicity assessment, USEPA relied upon the reproductive toxicity study of Exxon (1991) and adopted a different endpoint (reduced fertility/fecundity) than was used in their 2015 TSCA assessment for NMP (fetal body weight changes). There is at least one

significant design flaw in the critical study of Exxon (1991) that affects NMP dose estimates. Specifically, Exxon (1991) failed to adjust the concentrations of NMP in feed to reflect changes in food consumption that occur during pregnancy and lactation. As a result, the doses of NMP were significantly elevated during the period of lactation (e.g., dose rates during week 3 of lactation were 2- to 3-fold higher than during week 1 of lactation). The results of several follow-up reproductive toxicity studies, showing that effects on fertility and fecundity were not observed in rats exposed to dietary 50-500 mg/kg-day NMP when feed levels were appropriately adjusted for changes in food consumption (Thornton, 1999; Hellwig and Hildebrand, 1999), suggests that the design flaw noted above for Exxon (1991) may be of critical importance to the manifestation of the effects observed in rats exposed to the same dose range.

USEPA has done a nice job of characterizing the weight of evidence for other endpoints by relying upon the results of multiple studies. For example: (1) USEPA combined data sets for oral and inhalation exposures to NMP to assess the relationship for fetal resorptions; and (2) USEPA examined the relationships for oral, inhalation and dermal exposures to NMP to examine overall patterns for changes in fetal body weight. A similar approach is needed here for their characterization of the dose-response relationship for NMP and reproductive toxicity endpoints.

- ***Recommendation - For the sake of consistency and completeness, we recommend that USEPA consider similar treatment of data for potential effects on fertility and fecundity by placing the data of Exxon (1991) within the context of data collected from other reproductive toxicity studies, including those for dietary exposure (Thornton, 1999; Hellwig and Hildebrand, 1999) and inhalation exposure (Solomon et al., 1995).***

1.6 Early Life Susceptibility

In their chronic toxicity assessment, USEPA has assumed that the male fertility and female fecundity effects are attributable to early life exposures (page 34 of the *Benchmark Dose Modeling Supplemental File*), justifying the use of internal dose measures for young (50 g) rats to support benchmark dose modeling.
The rational for this assumption is unclear and problematic for several reasons, as described below.

- *Exposure Duration Effect* – Inspection of the BMD modeling results in Table 4-4 of USEPA's *Benchmark Dose Modeling Supplemental File* demonstrate a consistent pattern between points of departure for P2/F2A vs P2/F2B litters for endpoints in both male and female animals (**Table 5**).

Table 5. POD Values for Fertility/Fecundity in P2 Male and Female Rats (USEPA, 2019; based on BMD modeling of data from Exxon, 1991)

	PODs for Male Fertility (mg/L)	PODs for Female Fecundity (mg/L)

ED_006308_00000213-00039

Generation	BMD	BMDL	BMD	BMDL
P2/F2A	20.5	10.9	35.9	16.7
P2/F2B	14.2	7.64	17.5	8.4

Specifically, POD values for both male and female fertility were approximately 25-50% lower for these effects on P2/F2B litters when compared to P2/F2A litters. Similar differences were noted between litters for litter size. Because the duration of exposure to NMP is longer for P2 animals at their 2nd litter (P2/F2B) than it is for P2 animals at their 1st litter (P2/F2A) (i.e., P2 animals continue to be exposed to NMP between their 1st and 2nd litters), this pattern is consistent with a duration effect, not an early life-stage effect, on the reported reproductive effects. This pattern is in contradiction to USEPA's assumption of early-life susceptibility (i.e., if early life exposures are assumed to drive the adverse response, we would expect POD values for both litters to be the same). Without any specific evidence supporting a window of susceptibility analysis, it is typical to assume that any effects observed reflect the cumulative exposure to NMP.

- *PBPK-Derived Internal Dose* – USEPA used the PBPK model to predict internal doses of NMP for rats of different sizes (50 g to 450 g; Table 4-1 of the *Benchmark Dose Modeling Supplemental File*), which demonstrate a nearly 2-fold difference in internal dose as a function of rat size. By adopting an assumption of early life susceptibility, only the lowest internal doses (those for a 50 g rat, which corresponds to an age of approximately 3 weeks) were used as a basis for BMD modeling (while others were used to support sensitivity analyses). This assumption results in a nearly 2-fold increase in USEPA's estimate of NMP potency. Because male rats in the Exxon (1991) study grew to more than 700 g (i.e., well above the maximum weight of 450 g included in the table), the table should be expanded to include rat body weights above 450 g to provide full coverage of internal doses expected under the conditions of the study.
- *Applicability to Adult Consumer and Worker Exposures* – An assumption of early-life susceptibility for this endpoint is inconsistent with the exposure scenarios to which the assessment is applied. Because nearly all (except for incidental ingestion of NMP) of the exposure scenarios to NMP are for exposures to adult consumers and workers, endpoints that are assumed to be pertinent to early life exposures are not considered applicable.

- ***Recommendation – If USEPA continues to rely upon the Exxon (1991) study, based on these reasons we recommend that they: (1) expand the internal dose table (Table 4-1) to include doses for larger rats (e.g., up to 700 g); (2) use a cumulative or duration-weighted average dose of NMP over the total exposure period (pre-mating, mating, gestation, lactation) as the basis for BMD modeling; (3) revisit the assumption of early-life susceptibility for the assessment of fertility effects, or adopt a different endpoint that is more directly applicable to adult worker and consumer exposures (e.g., effects on fetal/pup body weights as done in USEPA, 2015).***

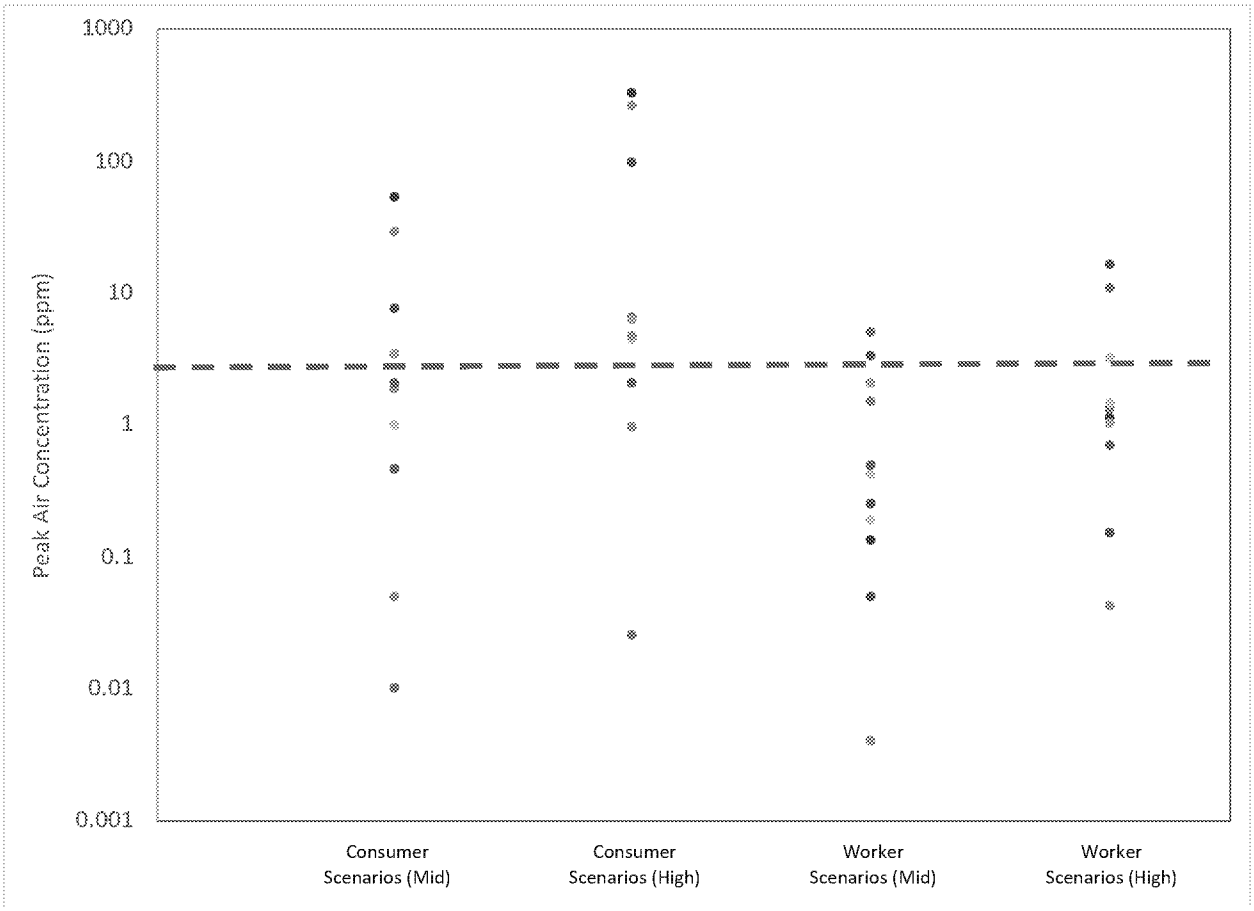
1.7 NMP-Specific Data for Metabolism in Humans Exposed to High Concentrations

ED_006308_00000213-00040

In estimating metabolism parameters in the PBPK model for NMP, USEPA has emphasized the fits of the model to low concentration data (2.5 ppm) of Bader and van Thriel (2006) at the expense of fits to data collected at higher concentrations (10 and 20 ppm) from the same study. This decision impacts multiple mid- and high-intensity exposure scenarios evaluated by USEPA for consumers and workers where exposures to air concentrations above 2.5 ppm were assessed (**Figure 3**):

- Consumer Scenarios (Mid) – Modeled peak concentrations of NMP in air exceed 2.5 ppm for 4 consumer scenarios (AdRemover, Degrease, Engine, LiqCleaner).
- Consumer Scenarios (High) – Modeled peak concentrations of NMP in air exceed 2.5 ppm for 7 consumer scenarios (Adhesives, AdRemover, Stain, Paint, Degrease, Engine, LiqCleaner).
- Worker Scenarios (Mid) – TWA concentrations of NMP in air exceed 2.5 ppm for 2 worker scenarios (Paint and coating removal, Auto).
- Worker Scenarios (High) – TWA concentrations of NMP in air exceed 2.5 ppm for 3 worker scenarios (Formulation, Paint and coating removal, Auto).

Figure 3. TSCA Exposure Scenarios with Peak Concentrations of NMP in Air Above 2.5 ppm

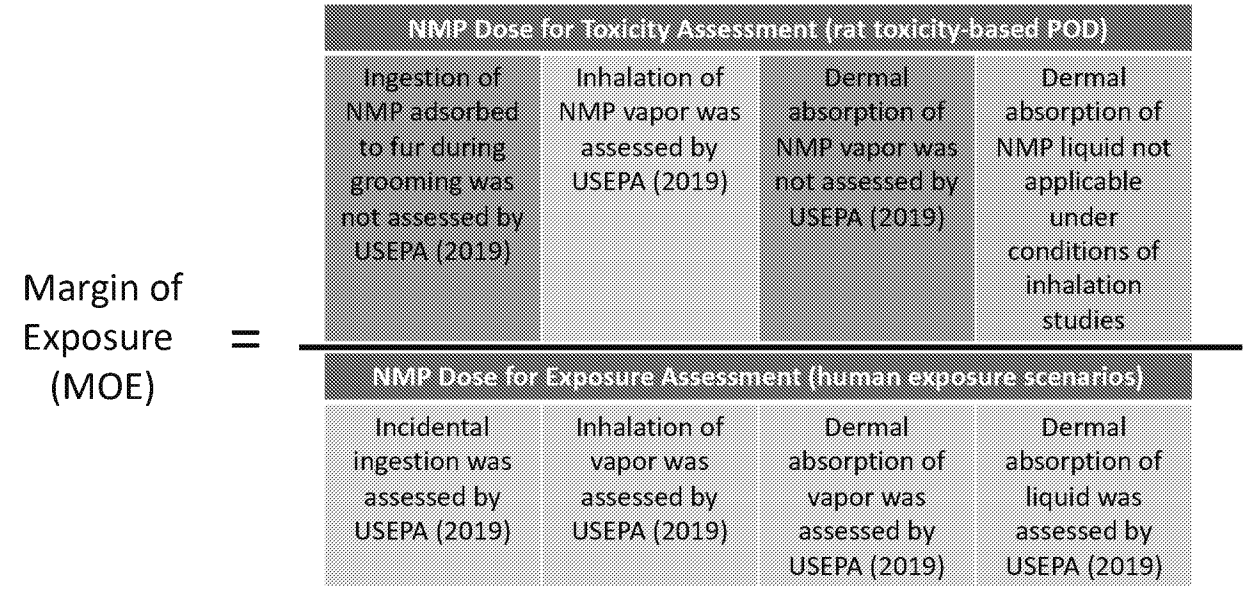


- ***Recommendation - Because future decisions made for NMP under TSCA are expected to be driven in part by the risks associated with high concentrations NMP in air (i.e., those above the dashed line in Figure 3), it is critical that the human PBPK model be appropriately parameterized for these exposure conditions. We recommend that USEPA either: (1) utilize all of the data from Bader and van Thriel (2006) to estimate a single set of parameters for describing NMP metabolism in humans; or (2) estimate two sets of metabolism parameters, one for low intensity exposures [<2.5 ppm, continuing to utilize the 2.5 ppm data from Bader and van Thriel (2006) alone], and another for high intensity exposures [>2.5 ppm, utilizing the 10 and 20 ppm data from Bader and van Thriel (2006)].***

1.8 Underestimation of NMP doses in rats exposed via whole body inhalation

USEPA considered up to 4 exposure pathways in their assessment of potential exposures to workers and consumers (incidental ingestion, inhalation of vapors, dermal absorption of vapors, dermal absorption of liquids). Inclusion of these pathways is appropriate in the human exposure assessment for NMP. However, this also introduces an inequitable treatment of NMP dose in the exposure and toxicity components of the margin of exposure (MOE) calculations for NMP, as is illustrated in **Figure 4**.

Figure 4. Illustration of Potential Mischaracterization of NMP Hazard in MOE Calculations (green = pathway quantified; red = pathway not quantified; grey = pathway not applicable)



Specifically, when USEPA used whole-body inhalation studies to derive PODs for acute and chronic effects, it considered only the inhalation of NMP vapor and not the contribution of other routes (i.e., dermal absorption of vapor and oral ingestion from grooming) to the internal dose even though it acknowledged that these other routes can contribute to the toxicity noted

ED_006308_00000213-00042

(USEPA, 2015 (pages 50 and 78); USEPA, 2019 (pages 173 and 205)) and included them in its human exposure assessment. By underestimating the numerator in the MOE calculation, the margin of exposure value calculated will be lower than its true value, and the magnitude of the underestimation is likely significant. As discussed in Poet et al. (2016), the exposure pathways issue is due in part to the PBPK model's reliance upon a nose-only inhalation study for model parameters. Specifically, air exposures to rats were parameterized in the PBPK model from a nose-only exposure study (Ghantous, 1995) and subsequently used to predict internal doses resulting from whole-body exposures to rats (Saillenfait et al., 2003; Solomon et al., 1995; Exxon, 1991). Therefore, in rats, model predictions for whole-body exposures for developmental toxicity studies do not include any contributions from dermal uptake of vapors or oral uptake via grooming (pathways depicted in red in **Figure 4**). If these pathways are sufficiently important to assess in humans, then these pathways are likely to be as important or more important to consider in the rat toxicity studies in which airborne concentrations of NMP are higher.

With respect to the dermal vapor pathway, there is clear NMP-specific data that this pathway is important. In humans exposed to NMP vapor, the combined contributions from inhalation and dermal absorption of vapor (when wearing trousers and short-sleeved shirts) to the internal dose were 1.5- (during moderate workload) to 1.7-fold (while at rest) higher than that from inhalation alone (Bader et al., 2008). In rats, whole-body exposures to NMP aerosol (inhalation, dermal, and ingestion pathways) achieved absorbed doses of NMP that were estimated to be approximately 4-fold higher than corresponding nose-only exposures (BASF, unpublished report). This result is consistent with rat skin being 2- to 3-fold more permeable to dermally applied NMP than human skin (USEPA, 2019). With respect to vapor exposures, McDougal et al. (1990) reported that the dermal permeability coefficients for organic chemical vapors were 2- to 4-times greater in rats compared to humans, suggesting the degree of impact for the dermal vapor pathway in rats could be even higher than that noted in humans.

With respect to sorption of vapors on to fur and ingestion while grooming, this pathway has been shown to be potentially significant for other chemicals, including 2-butoxyethanol (Poet et al., 2003), 1,1,2,2-tetrachloroethane (Gargas and Andersen, 1989), and ethylene glycol (Tyl et al. 1995). Because of grooming behavior in rats, the oral dose received from fur is expected to be considerably higher than the incidental ingestion of vapors in humans.

Poet et al. (2016) estimated that if these two pathways combine to increase the total NMP dose delivered to rats via whole-body exposures by a factor of 3.3-fold compared to vapor inhalation alone, the apparent discrepancy in NMP potency for oral vs. inhalation exposures for developmental toxicity would be resolved (i.e., concordance across route of exposure) (Poet et al., 2016). A factor of 3.3-fold is not unreasonable. Based on the 1.7-fold higher internal dose in humans due to the contribution from dermal absorption of NMP vapor as well as the 2- to 4-fold higher permeability of rat skin versus human skin, whole-body exposures of rats may result in a total dose that is 3.4- to 6.8-fold higher than that provided by inhalation of vapor alone.

ED_006308_00000213-00043

- ***Recommendation – We recommend that USEPA include quantification of these two pathways (dermal absorption of NMP vapors, ingestion of fur-adsorbed NMP from grooming) when deriving POD values from rat studies for inhalation exposures to NMP, so that any errors in MOE calculation are avoided. Such an approach would be consistent with USEPA's statement on page 173 that correctly notes that "A whole-body inhalation study in rats, which likely included dermal and oral uptake through grooming". At a minimum, we recommend that this important source of uncertainty be discussed in Section 4.3 of the risk assessment.***

2. Miscellaneous Items

BMDS Version

In USEPA's draft risk assessment for NMP they have relied upon several versions of their BMDS program. For the acute toxicity assessment based on the data of Saillenfait et al. (2002, 2003), BMDS 2.5 was used. There appear to be differences in the results returned by this version of BMDS when compared to the current version (3.1.2). Specifically, USEPA derived a BMDL01 value for the combined Saillenfait data set of 216 mg/L using BMDS 2.5 using a modeled variance. Using BMDS 3.1.2, modeled variance runs fail to return results for this data, while for runs assuming a constant variance a BMDL01 value of 229 mg/L is returned (slightly higher than 216 mg/L). Another difference noted is that the p-value for fit to the combined data is improved to 0.216 (compared to <0.0001 reported by USEPA using version 2.5). Because a low p-value can be used to argue against combining the oral and inhalation data from Saillenfait et al. (2002, 2003), this issue can have secondary consequences in the risk assessment.

- ***Recommendation - We recommend that USEPA rely upon the latest version of BMDS in their TSCA risk assessment for NMP. In addition, since variance does not appear to vary in a systematic manner as a function of dose, an assumption of constant variance should be considered.***

QA/QC

In an assessment as large and complex as the one prepared by USEPA for NMP, there are bound to be inconsistencies and errors. One example discussed above pertains to differences in the reported (1,013 mg/m^3) vs. used (1,800 mg/m^3) value for Csat in the air modeling conducted for consumer exposures. Another example is noted in Table 3-3-1 of the BMD supplemental file in which the number of litters cited in the table (for the 120 and 831 mg/L dose groups) differs from the values used in the BMD modeling. An exhaustive review of these types of inconsistencies/errors in the risk assessment and supporting documents is not possible within the time constraints of the public comment review period for this assessment, but it is likely that such an effort would reveal additional examples of errors and inconsistencies.

- ***Recommendation – We recommend that USEPA conduct a comprehensive QA/QC review of the risk assessment and supporting files to minimize potential errors and inconsistencies.***

ED_006308_00000213-00044

3. References

Bader, M., van Thriel, C., 2006. Human Volunteer Study on Biomarkers of N-methyl-2-pyrrolidone (NMP) After Inhalation Exposure (Report for the NMP Producers Group, Washington, DC).

Bader, M., Wrbitzky, R., Blaszkewicz, M., Schaper, M., van Thriel, C., 2008. Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch. Toxicol. 82, 13-20.

BASF. Unpublished. N-methylpyrrolidone: Interrelation of volatility (vapor concentration) and relative air humidity in inhalation studies; subacute inhalation toxicity of NMP-aerosols generated with different generation modes after after 2 - 4 weeks exposure of female rats in whole body inhalation chambers and head/nose inhalation systems.

Crook V, Simpson A. 2007. Protective glove selection for workers using NMP containing products - Graffiti removal. Health & Safety Laboratory, unpublished report. HSL/2007/41.

Gargas, M.L., Andersen, M.E. 1989. Determining kinetic constants of chlorinated ethane metabolism in the rat from rates of exhalation. Toxicol. Appl. Pharmacol. 99 (2), 344-353.

Ghantous, H. 1995. In Oral, Dermal, and Inhalation Pharmacokinetics and Disposition of [2-14 C] NMP in the Rat. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Wilmington, DE. Report for E.I.

Kirman CR. 2020. Using PBPK Modeling to Assess the Efficacy of Glove Materials in Reducing Internal Doses and Potential Hazards of N-MethylPyrrolidone During Paint Stripping. Submitted to the Journal for Exposure Science and Environmental Epidemiology.

Marquart, H; Franken, R; Goede, H; Fransman, W; Schinkel, J. (2017). Validation of the dermal 7152 exposure model in ECETOC TRA. Annals of Work Exposures and Health 61: 854-871.

McDougal, J.N., Jepson, G.W., Clewell 3rd, H.J., Gargas, M.L., Andersen, M.E., 1990. Dermal absorption of organic chemical vapors in rats and humans. Fundam. Appl. Toxicol. 14 (2), 299-308.

OECD. 2007. SIDS Initial Assessment Repor For SIAM 24, 19-20 April 2007, Paris, France: 1-methyl-2-pyrrolidone. Organisation for Economic Cooperation and Development.

Poet, T.S., Soelberg, J.J., Weitz, K.K., Mast, T.J., Miller, R.A., Thrall, K.D., Corley, R.A. 2003. Mode of action and pharmacokinetic studies of 2-butoxyethanol in the mouse with an emphasis on forestomach dosimetry. Toxicol. Sci. 71 (2), 176-189.

Poet TS, Schlosser PM, Rodriguez CE, Parod RJ, Rodwell RE, Kirman CR. 2016. Using physiologically based pharmacokinetic modeling and benchmark dose methods to derive an occupational exposure limit for N-methylpyrrolidone. Reg Toxicol Pharmacol 76: 102-112.

Saillenfait, A.M., Gallissot, F., Langonne, I., Sabate, J.P., 2002. Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats. Food Chem. Toxicol. 40, 1705-1712.

Saillenfait, A.M., Gallissot, F., Morel, G. 2003. Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure. Food Chem. Toxicol. 41, 583-588.

Schmidt VR. 1976. Experimental investigations about the embryotoxic and teratogenic effect of N-methyl-pyrrolidone. (German with English translation). Biol. Rund. 14:38-41.

Solomon, H.M., Burgess, B.A., Kennedy Jr., G.L., Staples, R.E. 1995. 1-Methyl-2-pyrrolidone (NMP): reproductive and developmental toxicity study by inhalation in the rat. Drug Chem. Toxicol. 18, 271-293.

Stull JO, Thomas RW, James LE. 2002. A comparative analysis of glove permeation resistance to paint stripping formulations. AIHA J (Fairfax, Va). 63(1):62-71.

ED_006308_00000213-00045

Summit Toxicology. 2017. Comments on USEPA's "Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]". Submitted to USEPA TSCA docket for NMP.

Tyl RW, Ballantyne B, Fisher LC, Fait DL, Dodd DE, Klonne DR, Pritts IM, Losco PE. 1995. Evaluation of the developmental toxicity of ethylene glycol aerosol in CD-1 mice by nose-only exposure. Fundam Appl Toxicol. 27(1):49-62.

USHUD. 2010. Monitoring of internal moisture loads in residential buildings. U.S. Department of Housing and Urban Development, Washington, DC.

USEPA. 2012. Benchmark Dose Technical Guidance. Risk Assessment Forum. U.S. Environmental Protection Agency. Washington, DC. EPA/100/R-12/001

USEPA. 1994. Consumer Exposure to Paint Stripper Solvents. MRI Report. EPA Contract 68-DO-0137.

USEPA. 2015. TSCA Work Plan Chemical Risk Assessment. N-Methylpyrrolidone: Paint Stripper Use CASRN: 872-50-4. Washington, DC: U.S. Environmental Protection Agency. EPA Document# 740-R1-5002.

USEPA. 2016. Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]. Washington, DC: U.S. Environmental Protection Agency.

USEPA. 2019a. Draft Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (NMP) CASRN: 872-50-4. U.S. Environmental Protection Agency. EPA-740-R1--8009

USEPA. 2019b. Draft Risk Evaluation for Methylene Chloride (Dichloromethane, DCM) CASRN: 75-09-2. U.S. Environmental Protection Agency. EPA-740-R1--8010

Van Raiij, M.T.M., Janssen, P.A.H., Piersma, A.H. 2003. The relevance of developmental toxicity endpoints for acute limit setting. RIVM report 601900004.

Zellers ET, Sulewski R. 1993. Modeling the temperature dependence of N-methylpyrrolidone permeation through butyl- and natural-rubber gloves. Am Ind Hyg Assoc J. 54(9):465-79.

Attachment 1: Using PBPK Modeling to Assess the Efficacy of Glove Materials in Reducing Internal Doses and Potential Hazards of N-MethylPyrrolidone During Paint Stripping

ED_006308_00000213-00047

Using PBPK Modeling to Assess the Efficacy of Glove Materials in Reducing Internal Doses and Potential Hazards of N-MethylPyrrolidone During Paint Stripping

CR Kirman, MS[1]

[1]Summit Toxicology, LLP, PO Box 3209, Bozeman, MT 59715; 406-224-0193; ckirman@summittoxicology.com

Key Words: PBPK, gloves, efficacy, risk assessment

Abstract. A refined risk assessment was conducted to evaluate the efficacy of different glove materials in reducing the potential hazards associated with using paint strippers containing N-methylpyrrolidone (NMP) under the scenarios defined by USEPA's TSCA risk assessment. Three categories of gloves were identified based on measured permeation rates for NMP: (1) minimal protection; (2) moderate protection; and (3) maximal protection. Simulations for eight acute and chronic occupational exposure scenarios identified by USEPA as having a potential hazard (i.e., margins of exposure, MOE, <30) were reassessed for each glove category using PBPK modeling to predict peak (Cmax) and cumulative (AUC) internal doses of NMP. For the acute assessment, the refined MOE values were ≥30 for half of the scenarios for gloves from the moderate protection group category, and all of the scenarios for gloves from the maximal protection category. For the chronic assessment, the refined MOE values were ≥30 for all scenarios except one for gloves from the maximal protection category. The results of this assessment indicate that: (1) the degree of protection provided by gloves from NMP permeation

ED_006308_00000213-00048

can vary widely depending upon the glove material, NMP formulation, and internal dose measure (with calculated glove protection factors ranging from 1.1 to 1900); and (2) NMP-containing paint strippers can be used safely when appropriate PPE are used. As such, these results can be used to support risk-reduction methods (e.g., product labeling, MSDS instructions on use of appropriate glove materials) as alternatives to banning NMP use under TSCA.

ED_006308_00000213-00049

1. Introduction

The Toxic Substances Control Act (TSCA), originally passed in 1976 and amended in 2016, provides EPA with authority to require reporting, record-keeping and testing requirements, and restrictions relating to chemical substances and/or mixtures. In March of 2015, USEPA released its final risk assessment for N-methylpyrrolidone (NMP) used in paint strippers under TSCA (1). In this assessment, USEPA evaluated acute and chronic exposure scenarios to workers and consumers using NMP-containing paint strippers. To support their assessment, USEPA relied upon several state-of-the-science tools/models, including physiologically based pharmacokinetic (PBPK) modeling, benchmark dose modeling, as well as a consideration of personal protective equipment (PPE) to reduce potential exposures. With respect to glove use, USEPA concluded the following:

> "*The use of gloves was determined to be effective in reducing modeled estimates of exposure, as demonstrated by the higher MOEs. For chronic exposure, gloves may not provide sufficient protection in all scenarios. More importantly, not all glove types are effective in protecting against NMP exposure. USEPA did not evaluate glove efficacy, however California DOH recommends the use of gloves made of butyl rubber or laminated polyethylene/EVOH2.*"

The efficacy of glove materials is an important factor to consider when evaluating methods for mitigating potential hazards from NMP exposure. Glove materials vary greatly in their effectiveness as a barrier to NMP, with measured permeation rates spanning nearly three orders of magnitude (2,3,4). For most of the exposure scenarios assessed by USEPA (all consumer

ED_006308_00000213-00050

scenarios, all nearby worker scenarios, and most central tendency worker scenarios) the margins of exposures (MOEs) calculated were deemed acceptable (i.e., MOE≥30). For eight central tendency and high-end worker scenarios, a potential unacceptable hazard was identified (i.e., MOE<30)(1). The goal of this work is to conduct a refined risk assessment for NMP use in paint strippers for these eight scenarios. Specifically, the efficacy of different glove materials was assessed using PBPK modeling to quantify the degree of protection offered under the conditions defined by the exposure scenarios developed by USEPA in their TSCA risk assessment for NMP.

2. Methods

USEPA's risk assessment for NMP utilized a margin of exposure (MOE) approach to characterize potential hazards. Use of PBPK modeling by USEPA permits this approach to be assessed in terms of internal dose estimates for toxicity and exposure:

$$MOE = ID_{TA} / ID_{EA} \qquad Eq.1$$

Where,

- MOE = Margin of exposure (unitless);
- ID_{TA} = Internal dose for the Point of Departure (POD) from the toxicity assessment for NMP (mg/L or mg*hr/L); and
- ID_{EA} = Internal dose from the exposure assessment for paint stripping scenarios for NMP (mg/L or mg*hr/L).

ED_006308_00000213-00051

Internal doses of NMP used by USEPA in their assessment include peak blood concentrations (Cmax, mg/L) to assess acute exposures, and area-under-the-curve (AUC, mg*hr/L) for NMP in blood to assess chronic exposures. MOE values for all consumer, nearby occupational, and low level occupational scenarios were calculated to be 30 or higher, where 30 is identified as an acceptable MOE value by USEPA [i.e., no concern for adverse effects of NMP if exposure (ID_{EA}) is at least 30-fold lower than toxicity (ID_{TA})]. These scenarios are not reassessed here. However, MOE values calculated for eight mid- and high-exposure level occupational scenarios were less than 30, with some calculated to be as low as 0.1. A summary of the results for the occupational scenarios (without gloves) from USEPA's risk assessment with MOE values less than 30 is provided in **Table 1**.

USEPA's toxicity and exposure assessment for NMP, along with a description of the refinements made for the dermal liquid pathway, are summarized below.

Summary of USEPA's Toxicity Assessment for NMP

The toxicity of NMP in laboratory animals has been well studied, with developmental effects consistently identified as the most sensitive endpoint for risk assessment purposes (1,5,6,7). The parent compound, rather than one of its metabolites, has been identified as the likely developmental toxin based on the results of *in vivo* and *in vitro* studies in rats (8,9). This conclusion supports the use of the parent chemical in blood as an appropriate measure of internal dose for characterizing the dose-response relationships for developmental effects.

ED_006308_00000213-00052

97 USEPA's toxicity assessment was adopted unchanged for this assessment, so that the focus
98 remains on the impact glove materials on potential hazards. USEPA modified a PBPK model
99 developed for NMP in rats (6) for the purposes of: (1) characterizing the dose-response relationship
100 for developmental effects in terms of internal dose; and (2) permitting the use of dose-response
101 data collected for oral and inhalation NMP exposures in a combined manner. Minor corrections
102 and modifications were made to the model code, as described in Appendix I of USEPA's
103 assessment (1). USEPA assessed endpoints for both acute and chronic exposures to NMP, as
104 summarized below and in **Table 2**.

105 • *Acute Exposures* - For acute exposures, USEPA identified fetal resorptions observed in rats
106 following oral gavage exposures to NMP (10), but not after inhalation exposures to NMP (11)
107 as the key endpoint of interest. The dose-response data for both oral and inhalation exposures
108 were combined and assessed in terms of peak concentration of NMP in maternal blood (Cmax,
109 mg/L). Based on the best fitting dose-response model (Hill) and a 1% benchmark response
110 rate, a point of departure value (BMDL01) of 216 mg/L was determined for fetal resorptions.

111 • *Chronic Exposures* - For chronic exposures, USEPA identified decreased fetal body weight
112 observed in rats following inhalation exposures to NMP (11) as the key endpoint of interest.
113 The dose-response data for inhalation exposures were assessed in terms of cumulative internal
114 dose of NMP in maternal rat blood (AUC, mg*hr/L). Based on the best fitting dose-response
115 model (linear) and a 5% benchmark response rate, a point of departure value (BMDL05) of
116 411 mg*hr/L was determined for fetal body weight decrements.

117

118 The two point of departure values summarized here (216 mg/L and 411 mg*hr/L) serve as the
119 numerators (ID_{TA}) for calculating acute and chronic MOE values in *Eq.1*. Additional analyses

ED_006308_00000213-00053

(i.e., use of other endpoints, dose measures, dose-response models) were performed by USEPA in support of the points of departure selected. Uncertainties associated with the selected points of departure are summarized in the discussion section.

Summary of USEPA Exposure Assessment for NMP

USEPA 's exposure assessment included consideration of three exposure pathways: (1) inhalation exposures to NMP vapors; (2) dermal exposure to NMP vapors; and (3) dermal exposure to NMP liquid. For this assessment, the first two exposure pathways remain unchanged, while the latter pathway was refined to permit a characterization of the effect of different glove materials on estimated internal doses of NMP. Acute exposures were assessed for both occupational and consumer scenarios, while chronic exposures were assessed only for occupational scenarios, since consumer scenarios are expected to be associated with short-term specific tasks. Occupational scenarios include miscellaneous stripping (low, mid, high exposures) and graffiti removal (low, mid, high exposures). Consumer scenarios include brush on (indirect, mid, and high exposures) and spray on (indirect and high exposures) applications either in a workshop or bathroom. The use of PPE (respirator and/or gloves) was varied to determine how this might affect exposure in both occupational and consumer scenarios. As stated above, only a subset of these scenarios (i.e., MOE<30) are considered here (as listed in **Table 1**).

For both acute and chronic exposure scenarios, USEPA relied upon a human PBPK model for NMP to calculate internal doses (i.e., corresponding to the denominator, ID_{EA}, in *Eq.1*). Internal dose estimates are expected to better represent exposures related to potential adverse effects (12). The human PBPK model for NMP allowed for aggregating exposures across multiple exposure

ED_006308_00000213-00054

routes/pathways, specifically dermal, vapor-through-skin, and inhalation exposures. The PBPK model was based on a published, peer-reviewed model (6) that was modified and validated for use by USEPA to support their risk assessment.

Exposure Assessment Refinements for Glove Use

A literature search was conducted to identify key studies and data sets for evaluating the permeation of NMP through glove materials. Three studies were identified and are summarized briefly below.

Zellers and Sulewski (2) assessed the temperature dependence of NMP permeation through different glove materials used in microelectronics fabrication facilities (ASTM F739-85 permeation test method). The butyl-rubber glove showed no breakthrough after four hours of exposure at any temperature, and NMP permeation was not detected at any time point. Breakthrough times and steady-state permeation rates for the other gloves, and their temperature dependence, were described. Permeation rates for NMP using glove materials other than butyl rubber ranged from 6 to 19 $\mu g/cm^2/min$.

Stull et al. (3) conducted a multiphase study to evaluate how gloves resist multichemical-based paint stripping formulations, including those that contain NMP. Twenty different glove types were identified for initial evaluation. Degradation resistance screening was carried out for each glove style and paint stripping formulation, and gloves least affected were identified. Gloves were then evaluated for their resistance to permeation using continuous contact testing (ASTM Test Method F 739), with those showing extensive permeation undergoing further testing for intermittent

ED_006308_00000213-00055

166 contact (modified form of ASTM Test Method F 1383). These results were used to select glove
167 styles to be tested using commercially available paint stripping products. Gloves made of plastic
168 laminate and butyl rubber were the most effective against the majority of paint strippers. The
169 authors concluded that more glove styles resisted permeation by NMP and dibasic ester-based
170 paint strippers than alternative solvent-based paint stripers such as methylene chloride, methanol,
171 isopropanol, acetone, and toluene. The authors also found that decreased contact time caused
172 relatively little change in permeation resistance and that the surrogate paint stripper data did not
173 always accurately predict resistance to the commercial paint stripper formulations. Permeation
174 rates for NMP using different glove materials were reported to vary by nearly three orders of
175 magnitude (<0.1 to 94 $\mu g/cm^2/min$).
176
177 Crook and Simpson (4) tested twenty glove types for their permeability to neat NMP and NMP-
178 containing formulations. Initial screening of gloves was performed by visual inspection and
179 gravimetric evaluation of solvent uptake over a 4-hour period. In the second phase, gloves were
180 evaluated for resistance to NMP permeation. Butyl rubber and laminate gloves generally offered
181 the greatest degree of protection from NMP permeation. Moderate permeation rates were observed
182 for polyethylene gloves. High permeation rates were observed for latex and nitrile gloves, with
183 some gloves exhibiting acute failure. Some variation in results across brands for the same glove
184 type and NMP formulations was observed. Overall, permeation rates for NMP using different
185 glove materials in this study were reported to vary by more than two orders of magnitude (<0.1 to
186 >34 $\mu g/cm^2/min$).
187

ED_006308_00000213-00056

NMP steady-state permeation rates as reported in the permeation studies (i.e., NMP flux, μg/cm^2-min) from these three studies are summarized in **Table 3**, and were used to calculate permeability coefficient (Kp, cm/hr) values, which are used to characterize dermal uptake in the PBPK model, using the following equation:

$$Kp = \frac{PR}{C} \times CF \qquad \text{Eq. 2}$$

Where,

Kp = permeability coefficient (cm/hr);

PR = permeation rate (μg/cm^2/min; **Table 3**)

C = NMP test concentration (mg/L; **Table 3**)

CF = conversion factor (0.001 mg/μg x 1000 cm^3/L x 60 min/hr)

Based on the data available for NMP permeation, three categories of glove materials were identified: (1) minimal protection (materials with permeation rates greater than 2 μg/cm^2-min); (2) moderate protection (materials with permeation rates between 1-2 μg/cm^2/min); and (3) maximal protection (materials permeation rates less than or equal to 0.3 μg/cm^2/min) (**Table 3**).

Net permeability coefficients for gloved hands were modeled as a multi-layered barrier consistent with Fick's law using the following equation, adapted from Solovyov and Goldman (12):

$$Kp_{net} = \frac{1}{\frac{1}{Kp_{skin}} + \frac{1}{Kp_{glove}}} \qquad Eq.3$$

Where,

Kp_{net} = net permeability coefficient for NMP through gloved skin (cm/hr; **Table 4**);

ED_006308_00000213-00057

Kp_{skin} = permeability coefficient for NMP through skin (0.00205 cm/hr for neat NMP; 0.000478 cm/hr for NMP solutions; USEPA, 2015); and

Kp_{glove} = permeability coefficient for NMP through glove material (cm/hr; **Table 3**).

Use of this equation conservatively assumes that there is no significant accumulation of NMP liquid between glove and skin, which would serve to reduce the concentration gradient and net permeation of NMP across the glove material. The mean and range of net permeability coefficients identified for each glove category (**Table 4**) were used to characterize NMP glove permeation in this risk assessment.

No changes were made to the PBPK model structure, parameter values (other than the refined Kp values), or assumptions defined by USEPA (1). For the eight exposures scenarios resulting in MOE values <30 (**Tables 1**), the PBPK model was used to simulate the impact of the net Kp values for gloved skin using different gloves types to assess their effect on predicted internal dose estimates. The internal doses and MOE values were compared to the values calculated by USEPA for exposure scenarios without gloves to assess glove material efficacy. To isolate the impact of gloves on the dermal liquid exposure pathway, PBPK simulations were also run for the eight occupational scenarios for the dermal liquid pathway alone (i.e., excluding inhalation and dermal vapor pathways) to calculate glove protection factor (PF) values for each glove category using the equation below:

$$PF = ID_{\text{no gloves}} / ID_{\text{gloves}} \qquad Eq.4$$

ED_006308_00000213-00058

Where,

PF = Protection factor (unitless);

$ID_{no\ gloves}$ = Internal dose for occupational simulations of the dermal liquid pathway without gloves (Cmax for NMP in blood, mg/L; AUC for NMP in blood, mg*hr/L); and

ID_{gloves} = Internal dose for occupational simulations of the dermal liquid pathway with gloves (Cmax for NMP in blood, mg/L; AUC for NMP in blood, mg*hr/L).

3. Results

MOE results for the acute exposure scenarios are provided in **Figure 1**. MOE values calculated for the moderate and maximum protection glove categories exhibit substantial improvement over the no-glove scenario values calculated by USEPA, while those calculated for minimum protection glove categories were minimally changed. Specifically, MOE values (rounded to 2 significant figures) calculated by USEPA for no-glove scenarios ranged from 0.7-14, while MOE values calculated for use of minimal, moderate, and maximum protection glove types range from 2-18, 16-67, and 86-910, respectively.

MOE results for the chronic exposure scenarios are provided in **Figure 2**. MOE values calculated for moderate and maximum protection glove categories again exhibit some improvement over the no-glove values calculated by USEPA, while those calculated for minimum protection glove categories were minimally changed. Specifically, MOE values (rounded to 2 significant figures) calculated by USEPA for no glove scenarios ranged from 0.1-6.1, while MOE values calculated

ED_006308_00000213-00059

for use of minimal, moderate, and maximum protection glove types range from 0.4-7.9, 4-30, and 24-410, respectively.

For both acute and chronic scenarios, by greatly reducing the contribution of the dermal liquid pathway to total internal dose, the refined MOE values for the maximal protection glove groups are driven primarily by the inhalation and dermal vapor pathways (i.e., glove use does not affect internal dose predictions arising from these pathways).

Glove protection factors calculated from PBPK simulations (isolated for the dermal liquid pathway) performed for the eight exposure scenarios indicate that the degree of protection to NMP permeation offered by gloves varies by several orders of magnitude, and depends on glove material, NMP formulation (NMP solution vs. neat NMP), and measure of internal dose (Cmax vs AUC) (**Table 4**).

4. Discussion/Conclusion

A refined risk assessment was conducted to assess the efficacy of different glove materials in reducing the potential hazards associated with use of NMP-containing paint strippers. For acute exposure scenarios, gloves from the minimum protection group (latex, nitrile) offered sufficient protection for all but one scenario assessed here, while gloves from the moderate and maximum protection groups offered sufficient protection for all scenarios. Although gloves from the minimum protection group may offer minimal protection when used on a task-specific basis (*e.g.*, short-term splash protection for acute consumer scenarios), their use cannot be

ED_006308_00000213-00060

recommended due to their risk of acute failure (swelling, splitting of material) (4), a factor not specifically evaluated in this assessment. For acute exposures to NMP-containing paint strippers, gloves from the moderate (polyethylene) and maximum (butyl, laminate) protection categories provide sufficient protection to workers (all MOE values ≥30). For chronic exposures to NMP-containing paint strippers, gloves from the moderate protection group (polyethylene) offered sufficient protection for half of the eight scenarios (i.e., the mid-level exposure scenarios), and gloves from the maximum protection group provided sufficient protection to workers for all scenarios except one in which an MOE of 24 was calculated (Miscellaneous Stripping (high-end), no respirator). The MOE value for this scenario is considered to approach a value of 30, and as discussed by Poet et al. (7) an MOE value of 21 may be considered adequately protective of a healthy worker population when a data-derived extrapolation factor for human toxicokinetic variation is adopted for NMP (see intraspecies variation discussion below).

The MOE values calculated in this assessment are higher than calculated for the no-glove scenarios in USEPA's TSCA risk assessment (1). The adoption of a number of health protective assumptions embedded in the assessment provide confidence that the MOE values calculated remain conservative. These assumptions include:

- *Constant Concentration of NMP in Liquid on Skin* – Consistent with the USEPA assessment, the concentration of NMP in liquid on skin or glove was assumed to be constant and infinite, rather than decrease over time due to absorption, volatilization, and transdermal flux of water (1). This is a conservative assumption that is intended to be

ED_006308_00000213-00061

protective of repeated dermal exposure events; however for non-glove scenarios this assumption can result in large predicted volumes of NMP taken up by the skin (e.g., up to 15 mL of NMP) over the course of a day. Modeling of the dermal liquid pathway as episodic in nature, with NMP concentrations decreasing over time or to amounts consistent with the use of finite volumes of strippers, is expected to result in lower, and more realistic exposure estimates.

- *Respirator Efficacy* – The efficacy of respirators at reducing inhalation exposures to NMP was not evaluated in this assessment. Instead, USEPA's assumption of a 90% reduction in the air concentration was maintained for this assessment. Like glove permeation rate, the efficacy of respirators is expected to vary. Bader et al. (13) assessed the efficiency of the facemasks with activated carbon filtering to prevent the inhalation of NMP vapors. The authors reported that gas samples taken from behind the face shield masks show no NMP detected over an 8-hour period of exposure to 80 mg/m^3 (20 ppm), which suggests that the MOE values calculated here for respirator use scenarios may be underestimated for high efficacy respirators. However, a comparison of MOE values for scenarios with and without respirator show very similar results (**Figures 1** and **2**), suggesting that inhalation of vapors was not a large contributor to total exposure.
- *Prolonged Dermal Contact with NMP* – USEPA's exposure scenarios for NMP included prolonged (up to 8 hours) and repeated dermal contact with NMP. Because NMP is considered to be irritating to eyes and skin (14), prolonged and repeated dermal contact with NMP, as assumed in this assessment, is expected to be self-limiting.
- *NMP Vapor Saturation* - Concentrations of NMP in air can become saturated at high concentrations (Csat), which is humidity-dependent and has been estimated to range from

ED_006308_00000213-00062

640 and 1,013 mg/m^3 for 50% and 0% relative humidity conditions, respectively. Although USEPA states in their risk assessment that Csat was considered in their air modeling simulations for NMP, inspection of the supporting material for USEPA's risk assessment reveals predicted air concentrations well above Csat for some simulations (e.g., as high as 7,771 mg/m^3)(1). By capping inhalation exposures at saturation limits, PBPK model simulations predict peak NMP in blood that are expected to be significantly lower than presented in USEPA's supplemental report (1).

- *Endpoint Selection* – Because the endpoint selected for NMP risk assessment (developmental effects) are applicable to exposures to pregnant women, MOE values for male and non-pregnant female workers exposed to NMP are expected to be higher than those calculated here, since they would be based upon on a less sensitive endpoint (i.e., higher POD values for effects other than developmental effects).
- *Human PBPK Model Parameterization* – In developing their PBPK model for NMP, USEPA relied upon conservative parameter values for humans using only the low-concentration data from the human volunteer study of Bader et al. (15) (rather than rely upon data from all concentration levels). This approach results in more conservative estimates for internal dose in humans by approximately 1.3- to 1.4-fold (7). This change alone would result in MOE values greater than 30 for all eight scenarios for gloves from the maximum protection category.
- *Rat PBPK Model Parameterization* – The rat PBPK model for inhalation exposures to NMP was parameterized based upon a study for nose-only exposures (16), while the inhalation toxicity studies for NMP involved whole-body exposures. For this reason, the internal dose estimates predicted by the PBPK model for inhalation POD values may be

ED_006308_00000213-00063

underestimated (i.e., thereby overestimating its toxic potency), since they do not include contribution for additional exposure pathways: (1) dermal uptake of NMP vapors, which has been shown to be significant for NMP in humans (14) and vapor permeability for other volatile chemicals is approximately 2- to 4-fold higher in rat skin compared to human skin (18); and (2) oral dosing from grooming of NMP vapor adsorbed to rat fur, which has been shown to be significant for other chemicals (17,18,19).

- *Intraspecies Variation* – An acceptable MOE value of 30 was defined by USEPA (1) for NMP, based upon consideration of interspecies differences in toxicodynamics (factor of 3), and intraspecies differences in toxicokinetics and toxicodynamics (factor of 10). However, an evaluation of human variation in toxicokinetics for NMP based on data from Bader et al. (16) suggests that MOE values of 20-21 (i.e., replacing a default factor of 3 for toxicokinetic variation, with a data-derived value of 2-2.1) may be considered protective for 95% of individuals from a healthy worker population (7). This change alone would result in acceptable chronic MOE values for 3/8 scenarios for moderately protective gloves and 8/8 scenarios for maximally protective gloves.
- *Benchmark Response Rate* – For the acute assessment, the use of a benchmark response rate of 1% for developmental effects is lower than has been selected for other chemicals, which typically rely upon a benchmark response rate of 5% or equivalent to one standard deviation. In this case, use of benchmark response rate of one standard deviation would results in an acute POD (ID_{TA}) and corresponding MOE values that are approximately 2.5-fold higher than those calculated here. Similarly, use of a benchmark response rate of one standard deviation would result in a 1.1-fold change in chronic POD and MOE values. This change alone would result in acceptable acute MOE values for all scenarios

ED_006308_00000213-00064

for glove from the moderately and maximally protective categories, while chronic MOE value conclusions remain unchanged.

- *Exposure Duration Concordance* - There is some degree of discordance in the exposure durations used in acute toxicity and acute exposure assessments conducted for NMP. Specifically, the point of departure for acute endpoints relies upon observations following a 15-day exposure to NMP, which covers the majority of the rat gestation period (21 days). On the other hand, the exposure duration assumed for acute exposures to workers (1 day) reflects a small fraction of the human gestation period (40 weeks). Based upon the concentration*time data for fetal resorptions in mice exposed to NMP (20), a one-day exposure to NMP would need to be significantly higher to produce an equivalent response for a 15-day exposure.

Refinements to the NMP risk assessment that address combinations of these conservative assumptions would be expected to result in MOE values that are considerably higher than calculated in this assessment, by perhaps as much as an order of magnitude or more. Such refinements would be consistent with USEPA's definition for Reasonable Maximum Exposure (RME) (21), which should contain an appropriate mixture of upper-bound and average values for exposure assumptions.

The results of this refined risk assessment indicate that NMP-containing paint strippers can be used safely, provided that appropriate PPE (i.e., gloves made of NMP-resistant materials in the maximum protection category) are used. In this assessment, use of gloves from the maximum protection category reduced internal dose estimates of NMP following acute and chronic

ED_006308_00000213-00065

exposures by more than 90%, indicating that the dermal absorption of liquid NMP is the most important pathway contributing to total exposure to workers in the eight scenarios evaluated. These results can be used to support risk-reduction methods as pragmatic alternatives to banning the use of NMP paint strippers under TSCA, including better instructions (for inclusion in MSDS, product labeling) regarding the use of appropriate glove material when using NMP paint strippers.

Acknowledgments: The author would like to thank Dr. Torka Poet for PBPK modeling support for this paper, and to Dr. Sean Hays for comments and discussions on the draft manuscript.

Conflict of interest: The author is an independent consultant affiliated with Summit Toxicology. This paper was prepared with financial support to Summit Toxicology from the NMP Producers Group, a group of companies and organizations that produce or use NMP. The NMP Producers Group was given the opportunity to comment on the manuscript, while the author retained final decision-making, and has the sole responsibility for the contents of this paper.

5. References

1. USEPA. 2015. TSCA Work Plan Chemical Risk Assessment N-Methylpyrrolidone: Paint Stripper Use. CASRN: 872-50-4. U.S. Environmental Protection Agency, Office of Chemical Safety and Pollution Prevention. EPA Document# 740-R1-5002.
2. Zellers ET, Sulewski R. 1993. Modeling the temperature dependence of N-methylpyrrolidone permeation through butyl- and natural-rubber gloves. Am Ind Hyg Assoc J. 54(9):465-79.
3. Stull JO, Thomas RW, James LE. 2002. A comparative analysis of glove permeation resistance to paint stripping formulations. AIHA J (Fairfax, Va). 63(1):62-71.

ED_006308_00000213-00066

4. Crook V, Simpson A. 2007. Protective glove selection for workers using NMP containing products - Graffiti removal. Health & Safety Laboratory, unpublished report. HSL/2007/41. http://www.hse.gov.uk/research/hsl_pdf/2007/hsl0741.pdf
5. OECD (Organization for Economic Cooperation and Development), 2007. SIDS Initial Assessment Profile: 1-methyl-2-pyrrolidone. SIAM 24, 19e20 April. Available at: http://webnet.oecd.org/Hpv/UI/SIDS_Details.aspx?id¼996F9CEA-4B30-4E70-9E54-8DEF28E023EB.
6. Poet, T.S., Kirman, C.R., Bader, M., van Thriel, C., Gargas, M.L., Hinderliter, P.M., 2010 Quantitative risk analysis for N-methyl pyrrolidone using physiologically based pharmacokinetic and benchmark dose modeling. Toxicol. Sci. 113 (2), 468-482.
7. Poet TS, Schlosser PM, Rodriguez C, Parod RJ, Rodwell DE, Kirman CR. 2016. Using physiologically based pharmacokinetic modeling and benchmark dose methods to derive an occupational exposure limit for N-methylpyrrolidone. Regulatory Toxicology and Pharmacology 76 (2016) 102-112.
8. Saillenfait, A.M., Sabate, J.P., Gallissot, F., 2007. Comparative developmental toxicities of the three major metabolites of N-methyl-2-pyrrolidone after oral administration in rats. J. Appl. Toxicol. 27, 571e581.
9. Flick B, Talsness CE, Jäckh R, Buesen R, Klug S. 2009. Embryotoxic potential of N-methyl-pyrrolidone (NMP) and three of its metabolites using the rat whole embryo culture system. Toxicol Appl Pharmacol. 2009 Jun 1;237(2):154-67.
10. Saillenfait, A.M., Gallissot, F., Langonne, I., Sabate, J.P., 2002. Developmental toxicity of N-methyl-2-pyrrolidone administered orally to rats. Food Chem. Toxicol. 40, 1705-1712.
11. Saillenfait, A.M., Gallissot, F., Morel, G., 2003. Developmental toxicity of N-methyl-2-pyrrolidone in rats following inhalation exposure. Food Chem. Toxicol. 41, 583-588.
12. Solovyov SE, Goldman AY. 2004. Permeability of multilayer structures. e-Polymers 2004, no. 023. ISSN 1618-7229.
13. Bader M, Wrbitzky R, Blaszkewicz M, Schäper M, van Thriel C. 2008. Human volunteer study on the inhalational and dermal absorption of N-methyl-2-pyrrolidone (NMP) from the vapour phase. Arch Toxicol. 82(1):13-20.
14. HSDB. 2019. Hazardous Substance Data Bank. http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+5022

ED_006308_00000213-00067

15. Bader M, Wrbitzky R, Blaszkewicz M, van Thriel C. 2007. Human experimental exposure study on the uptake and urinary elimination of N-methyl-2-pyrrolidone (NMP) during simulated workplace conditions. Arch Toxicol. 2007 May;81(5):335-46.
16. Ghantous, H., 1995. In Oral, Dermal, and Inhalation Pharmacokinetics and Disposition of [2-14 C] NMP in the Rat. Report for E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Wilmington, DE.
17. McDougal, J.N., Jepson, G.W., Clewell 3rd, H.J., Gargas, M.L., Andersen, M.E., 1990. Dermal absorption of organic chemical vapors in rats and humans. Fundam. Appl. Toxicol. 14 (2), 299-308.
18. Gargas ML, Andersen ME. 1989. Determining kinetic constants of chlorinated ethane metabolism in the rat from rates of exhalation. Toxicol Appl Pharmacol. 1989 Jun 15;99(2):344-53.
19. Poet, T.S., Soelberg, J.J., Weitz, K.K., Mast, T.J., Miller, R.A., Thrall, K.D., Corley, R.A., 2003. Mode of action and pharmacokinetic studies of 2-butoxyethanol in the mouse with an emphasis on forestomach dosimetry. Toxicol. Sci. 71 (2), 176-189.
20. Schmidt VR.1976. Experimental investigations about the embryotoxic and teratogenic effect of N-methyl-pyrrolidone (NMP). Biologische Rundschau 14, 38-41.
21. USEPA. 1989. Risk assessment guidelines for superfund. Volume 1. Human health evaluation manual (Part A). EPA/540/1-89/002.

ED_006308_00000213-00068

462 **Table 1. Select No-Glove Occupational Exposure Scenarios for NMP Paint Stripper Use**
463 **Under TSCA(1)[1]**

			Estimated Margin of Exposure	
Exposure Scenario	**Exposure Level (NMP Liquid Exposure)**	**Respirator use**	**Acute**	**Chronic**
Miscellaneous Stripping	Mid-range (NMP Solution)	-	12.7	5.4
		+	13.7	5.9
	High-end (Neat NMP)	-	0.7	0.1
		+	0.7	0.1
Graffiti Removal	Mid-range (NMP Solution)	-	14.1	6.1
		+	14.1	6.1
	High-end (Neat NMP)	-	0.7	0.1
		+	0.7	0.1

464 [1]Only exposure scenarios identified with potential hazard (i.e., MOE<30) are included here.

ED_006308_00000213-00069

465 **Table 2. Summary of NMP Toxicity Values Expressed in Terms of Internal Dose**

Assessment Decision	**Acute Assessment**	**Chronic Assessment**
Endpoint (Key Study)	Increased incidence of fetal resorptions in rats (Saillenfait et al.,10,11)	Decreased fetal body weights in rats (Saillenfait et al., 11)
Internal Dose	Cmax	AUC
Benchmark Dose Model	Hill	Linear
Benchmark Response Rate	1%	5%
Point of Departure	BMDL01 = 216 mg/L	BMDL05 = 411 mg*hr/L

466

467

ED_006308_00000213-00070

468 **Table 3. Summary of NMP Permeation Rates for Various Glove Materials**

Glove Category	Glove Material	Glove Brand	Test Material	Permeation Rate (µg/cm²/min)[1]	NMP Test Concentration (mg/cm³)	Permeability Coefficient (cm/hr)[2]	Reference
Minimal Protection	Refinishing gloves (natural rubber)	Thompson & Forby	NMP Formulation IV	**94**	773	0.0073	Stull et al. (3)
			Stripper IV-B	**14**	381	0.0022	
			NMP Formulation V	7.7	515	0.00090	
			Stripper IV-A	6.6	690	0.00057	
			NMP Formulation VI	0.19	371	0.000031	
	Nitrile	Kimberly-Clark Safeskin 52002M	NMP	>34	1030	0.0020	Crook and Simpson (4)
		Ansell Solvex 37-675	NMP	32	1030	0.0019	
	Latex	Ansell Conform 69-150	NMP	>26	1030	0.0015	
		Ansell	NMP	39	1030	0.0023	Zellers and Sulewski (2)
		Edmont Puretek	NMP	16	1030	0.00093	
	Latex/neoprene / nitrile	Pioneer Trionic	NMP	17	1030	0.00099	
Moderate Protection	Polyethylene	Ansell Profood 35-405	Graffiti Gone CR-GR1	**1.6**	464	0.00021	Crook and Simpson (4)
			NMP	1.2	1030	0.000070	
Maximum Protection	Butyl	North	Stripper IV-B	**0.3**	381	0.000047	Stull et al. (3)
		KCL Butoject 898	NMP	<0.1	1030	0.0000029	Crook and Simpson (4)
			Graffiti Gone CR-GR1	<0.1	464	0.0000065	
		Comasec	NMP Formulation IV	<0.1	773	0.0000039	Stull et al. (3)
			NMP Formulation V	<0.1	515	0.0000058	
			NMP Formulation VI	<0.1	371	0.0000081	
		Guardian	NMP Formulation IV	<0.1	773	0.0000039	
			NMP Formulation V	<0.1	515	0.0000058	
			NMP Formulation VI	<0.1	371	0.0000081	
		North	NMP Formulation IV	<0.1	773	0.0000039	

ED_006308_00000213-00071

			NMP Formulation V	<0.1	515	0.0000058	
			NMP Formulation VI	<0.1	371	0.0000081	
			Stripper IV-A	<0.1	690	0.0000043	
			NMP	Not detected	--	--	Zellers and Sulewski (2)
	Laminate	North Silver Shield	NMP	<0.1	1030	0.0000029	Crook and Simpson (4)
		North Silver Shield	Graffiti Gone CR-GR1	<0.1	464	0.0000065	
		Safety 4	NMP Formulation IV	<0.1	773	0.0000039	Stull et al. (3)
			NMP Formulation V	<0.1	515	0.0000058	
			NMP Formulation VI	<0.1	371	0.0000081	
			Stripper IV-A	<0.1	690	0.0000043	
			Stripper IV-B	<0.1	381	0.0000078	

[1]Maximum values for each category in bold were used to represent the glove group for PBPK simulations.

[2]Permeability coefficient = Permeation rate / NMP Concentration * Conversion factor (1 mg/1000 ug)*(1000 cm3/L); For nondetect permeation rates (e.g., <0.1), a value of ½ the detection limit was used (e.g., 0.05).

Table 4. NMP Glove Protection Factors Calculated for Different Glove Materials

Liquid NMP Exposure	Glove Category	Net Permeability Coefficient for Gloved Skin (cm/hr)[1]	Protection Factors for Specific Internal Dose Measures[2]	
			Cmax	AUC
NMP Solution	Minimal Protection	0.00038 (0.000029-0.00045)	1.3 (1.1-18)	1.3 (1.1-18)
	Moderate Protection	0.00011 (0.000061-0.00015)	4.7 (3.5-8.4)	4.9 (3.6-8.7)
	Maximal Protection	0.0000076 (0.0000029-0.000043)	68 (12-180)	71 (12-190)
Neat NMP	Minimal Protection	0.00098 (0.000030-0.0016)	2.5 (1.3-130)	3.0 (1.4-180)
	Moderate Protection	0.00013 (0.000068-0.00019)	28 (18-56)	39 (26-78)
	Maximal Protection	0.0000077 (0.0000029-0.000046)	510 (83-1400)	720 (120-1900)

[1]Value reflects the mean for the glove category calculated using Eq.3. Range of values indicated in parentheses.

[2]Value reflects the mean for the glove category calculated using Eq.4. Range of values indicated in parentheses.

ED_006308_00000213-00073

Figure 1. Margins of Exposure for Acute Exposure Scenarios Using Different Glove Types. Columns indicate the mean value for the glove category, error bars indicate the range for the glove category.

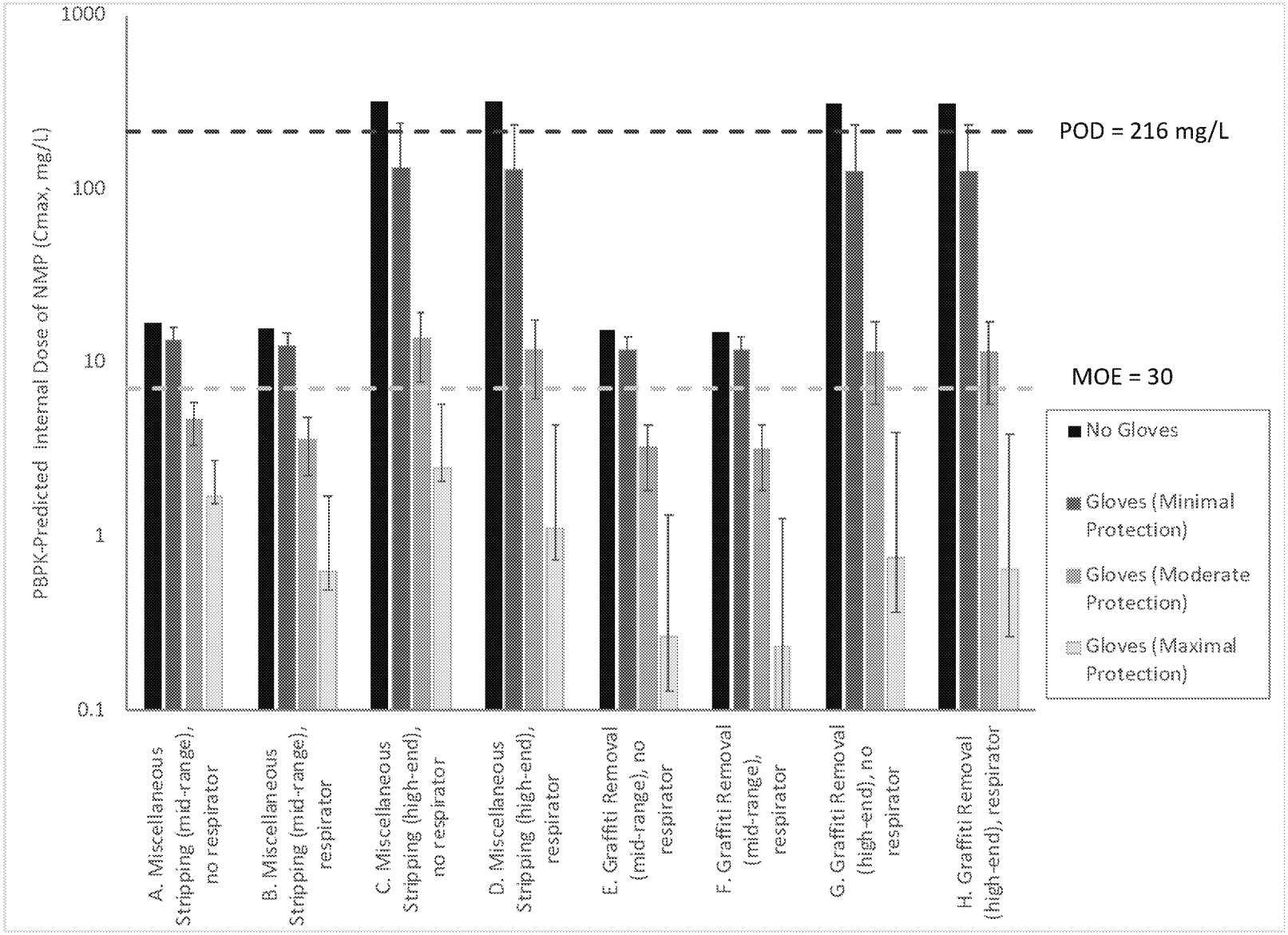


Figure 2. Margins of Exposure for Chronic Exposure Scenarios Using Different Glove Types. Columns indicate the mean value for the glove category, error bars indicate the range for the glove category.